HOW COULD THE DETAILED MAPPING OF HUMAN CELLS CONTRIBUTE TO EARLY DISEASE DETECTION AND PREVENTION EFFORTS? – Soham Kale

INTRODUCTION:

My parents simply refused to use Google Maps when travelling, and then always ended up in the completely wrong place after taking the wrong exit on the motorway roundabout. Taunting them, saying "Using Google Maps wouldn't have hurt" felt good.

Notice how my family and I could've ended up at two completely different places from the same roundabout? In the same way, the same biological pathway could lead to diseases ranging from schizophrenia to autism.
All diseases are fundamentally mechanical problems at a genetic and molecular level, interacting with cells via an interconnected biological pathway.
Cell mapping (Google Maps) allows us to unravel these biological pathways (roads), creating opportunities for efficient, directed treatment so that my family doesn't get lost again.

Single-cell RNA sequencing (scRNA-seq) is vital in unravelling heterogeneity in tissues, proving similar cells in the same tissue vary in their function due to differences in their genetic composition. As a result, precision medicine has made substantial advancements, creating a foundation allowing for more precise diagnosis, and more effective treatments.

Proceed to the route.

X MARKS THE SPOT:

Cell mapping has allowed for more accurate developmental analysis and effective treatment of health and disease through the discovery of new cell types and how they interact with the human body. The newly discovered gut metaplastic cell was found to have connections with inflammatory bowel disease [1], creating a positive feedback loop where this

[1] Oliver, A.J., Huang, N., Bartolome-Casado, R., Li, R., Koplev, S., Nilsen, H.R., Moy, M., Cakir, B., Polanski, K., Gudiño, V., Melón-Ardanaz, E., Sumanaweera, D., Dimitrov, D., Milchsack, L.M., FitzPatrick, M.E.B., Provine, N.M., Boccacino, J.M., Dann, E., Predeus, A.V. and To, K. (2024). Single-cell integration reveals metaplasia in inflammatory gut diseases. *Nature*, [online] 635(8039), pp.699–707. doi:https://doi.org/10.1038/s41586-024-07571-1.

inflammation led to further metaplasia. Through the Human Cell Atlas, it was also found that some cells appear to be the culprit in multiple diseases including cystic fibrosis. Uncovering such cells that play roles in both acute and chronic conditions creates opportunities for drug intervention, unravelling the root cause of disease.

Therefore, cell discovery has allowed for the establishment of more specific therapies which strategically defeat diseases. After a placenta was mapped, an opportunity for the development of pregnancy-specific treatment was discovered as it was found that the fetal Hofbauer immune cell was activated in toxoplasmosis, listeria and malaria[2]. *T-gondii* (the parasite that causes toxoplasmosis) was found to evade immune response by infiltrating and using the Hofbauer cells; this further reinforces the idea that the root cause for many types of infection can be discovered through cell mapping, helping reduce pregnancy complications by targeting these cells in this example, again providing opportunity for drug intervention, allowing for better prevention of the manifestation of disease.
JACKPOT. The map didn't lie!

WE'RE ALL DIFFERENT, SO ARE OUR CELLS:

10 years old, I was sent to the GP with a nasty illness diagnosed to be tonsilitis. "Not this again," I thought to myself as the doctor prescribed me with the same old Amoxicillin antibiotics for my infection that were also given for my mother for her ear infection. "Everybody receives the same medicine, is this treatment even effective?" I said.

It is.
But only 30-60%[3] of the time.

Instead, individual characterisation of the underlying cause of disease allows for the innovation of personalised treatments to match immune response based on an individual's genetic makeup. This is done through identifying gene patterns and predisposition markers using scRNA-seq, investigating their influence on cellular heterogeneity which leads to

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[2] Sanger.ac.uk. (2020c). *Source of pregnancy complications from infections revealed by placenta map*. [online] Available at: https://www.sanger.ac.uk/news_item/source-of-pregnancy-complications-from-infections-revealed-by-placenta-map/ [Accessed 29 Jan. 2025].

[3] NHS England (2022). *Accelerating genomic medicine in the NHS*. [online] www.england.nhs.uk. Available at: https://www.england.nhs.uk/long-read/accelerating-genomic-medicine-in-the-nhs/.

diseases such as cancer. After carrying out the scRNA-seq of breast cancer cells, analysing the tissue helped compartmentalise and identify 41 different clusters of cells, from which immune cells from BRCA1 and BRCA2 mutation carriers were found, proving the strong genetic influence on disease. These carriers displayed unique immune cell gene expression pathways where genes were either active or inactive, leading to changes in the immune cell's functional potency. It was found that macrophage cells underwent immune exhaustion; they were less effective in recognising and eliminating abnormal cells due to their impaired cytotoxic function. Therefore, immune changes in healthy breast tissue led to the immune system 'escaping detection', which started early before the tumours formed. This provides opportunity for the preliminary detection of biomarkers for early disease detection, which can be done through implementing regular biopsies of individuals at high risk of disease due to external factors such as age, family history and parity. Incorporating an 'early warning system' in healthcare in this way aids in preventing disease before its onset and manifestation, such as cancer in this case. This provides earlier, faster and more precise diagnosis to reduce diagnostic odyssey, reducing uncertainty in patient treatment allowing them to benefit from more treatment possibilities due to earlier diagnosis. Moreover, the individual characterisation of the underlying cause of disease informed by genomics through a multidisciplinary approach creates tailored treatment to match an individual's molecular makeup to make clinical response more effective. This strategy far outshines the typical symptom-driven, broad diagnosis often given to patients, offering a more precise and impactful solution.

REROUTING:

Ever took a wrong turn and heard the word 'rerouting' as Google Maps works hard to find the quickest combinations of pathways to get you to your destination to combat traffic? In the same way, researchers observe infection pathways and mechanisms to combat disease. This is done through manipulating the aforementioned understanding on cellular heterogeneity by mapping cells to create a reference for understanding human health while diagnosing, monitoring and treating disease. As soon as these mechanisms are understood, potential drug targets are highlighted, allowing preventive drugs to be formulated to create safe therapies for disease. To illustrate, it was discovered that *mycobacterium tuberculosis* carries out immune evasion through evolving strategies to survive and replicate within macrophages[4]. This insight into the infection pathways leading to tuberculosis lays a foundation to provide better treatment going into the future.
This understanding also allows for the management of global disparities in disease prevention, making a positive impact on sociological equity in healthcare through formulating spatially specific treatment:
It was discovered that HIV mechanisms vary across the globe. For example, those in Malawi

[4] Stanley, S.A. and Cox, J.S. (2013). Host-pathogen interactions during Mycobacterium tuberculosis infections. *Current Topics in Microbiology and Immunology*, [online] 374, pp.211–241. doi:https://doi.org/10.1007/82_2013_332.

are different to other places, because varying environmental exposures were found to affect disease pathobiology[5].

THE POSITIVE MULTIPLIER EFFECT – AN ECONOMICAL STANDPOINT:

Through unravelling cellular heterogeneity, present-day generalised treatment in response to disease will be transformed forever. Classifying, characterising and distinguishing each cell on a transcriptome level helps us observe patterns in immune activity. Thus, identifying biomarkers facilitates healthcare advancement by reducing long-term monetary costs through research.
Investigation into chemotherapy-resistant cancer cells by using single-cell mapping techniques found that cancer mutations fell into four categories. Three of these were:
1) Drug addiction mutations (cancer cells use the drug to help them grow).
2) Drug resistance mutations (genetic changes in the cancer cell lead to the drug being less effective).
3) Driver mutations (genetic changes allow cancer cells to use a different signalling pathway to grow, resisting the pathway that the drug has blocked)[6].
Combining the discovery of specific pathways and pharmacological approaches will construct drug combinations that 'yield more penetrant and lasting responses in patients[7]'.
Along with the identification of these potential second-line therapies, these insights help save invaluable capital due to less squandered funds on the development of futile drugs.
This allows researchers to channel funding into the right areas, leading to better disease prevention over the long-term by discovering new methods of treatment earlier.
Consequently, saving capital allows more resources to be reinvested into further research, enhancing global healthcare and patient outcomes in the long run.
This, therefore, creates a positive multiplier effect.
In addition, determining the specific treatment required by observing biological pathways saves both crucial time and lives.

CONCLUSION:

[5] Nyirenda, J., Hardy, O.M., Filho, S., Herder, V., Attipa, C., Ndovi, C., Siwombo, M., Rex, N.T., Suwedi, L., Ilia, G., Nyasulu, W., Ngulube, T., Nyirenda, D., Mvaya, L., Phiri, J., Chasweka, D., Eneya, C., Makwinja, C., Phiri, C. and Ziwoya, F. (2024). Spatially resolved single-cell atlas unveils a distinct cellular signature of fatal lung COVID-19 in a Malawian population. *Nature Medicine*, [online] pp.1–13. doi:https://doi.org/10.1038/s41591-024-03354-3.

[6] European Bioinformatics Institute (2024). Cancer drug resistance causes and categories identified. *Ebi.ac.uk*. [online] doi:https://doi.org/10-2024/2024-Open-Targets-Cancer-Categories-1000x600-1.

[7] Wood, K.C. (2015). Mapping the Pathways of Resistance to Targeted Therapies. *Cancer Research*, 75(20), pp.4247–4251. doi:https://doi.org/10.1158/0008-5472.can-15-1248.

After years of struggle, my parents have finally pledged to make best use of Google Maps after reading this essay. I am ecstatic to announce that our average journey times have drastically improved, and the Kale family will no longer end up in Liverpool when trying to reach our neighbour's house. I would like to give an expression of gratitude to the Human Cell Atlas in providing me and my family with a sense of direction in our lives.

Human cell mapping is revolutionising long-term disease prevention by enabling the development of more targeted and precise treatments through the analysis of genetic patterns and infection pathways. By uncovering the complexities of cellular heterogeneity, it has significantly enhanced early disease detection. This has led to improved patient outcomes both in the short term through potential earlier diagnosis, and in the long run through the provision of a wider variety of treatment options. This breakthrough has, and will continue to create a powerful ripple effect within the healthcare system, driving global growth and transforming healthcare for all.

As an aspiring doctor, I am eager to be part of the pivotal future of precision medicine, where innovation and individualised care will redefine healthcare.

You have arrived at your destination!

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