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# Drug-resistant cell lines in cancer

Jindrich Cinatl Jr, Mark N. Wass & Martin Michaelis

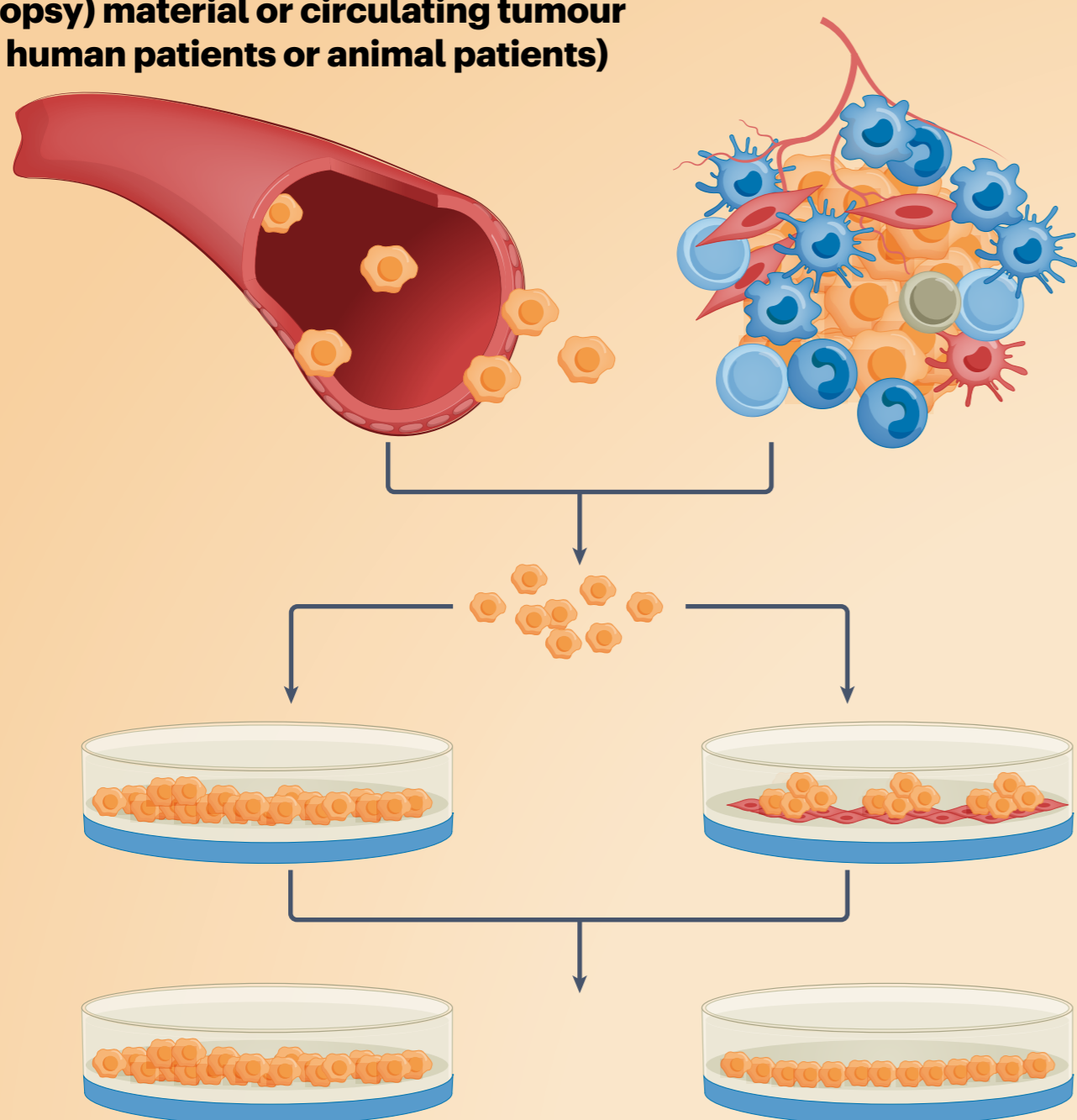
The occurrence of therapy resistance is the major reason for treatment failure in cancer. Resistance can be intrinsic or acquired. Conceptually, intrinsic resistance results from pre-existing resistance mechanisms, whereas acquired resistance results from directed evolution in response to the selection pressure imposed by anticancer therapies. To study acquired resistance, model systems are needed that reflect the evolutionary processes underlying resistance

formation – most commonly, drug-adapted cancer cell lines. Three main methods are used to establish drug-resistant cell lines: continuous cell line exposure to stepwise increasing drug concentrations; pulsed treatment where exposure to the drug is alternated with recovery periods in drug-free medium; and one-step selection of pre-existing resistant subpopulations in a cancer cell line using a (comparatively) high drug concentration.

## Establishment of cancer cell lines from tumour material

Tumour material is dispersed and cultured in the absence (left) or the presence (right) of a feeder layer (typically inactivated fibroblasts) until it develops into a permanent cell line, which may grow as a monolayer, in agglomerates and/or as non-adherent culture.

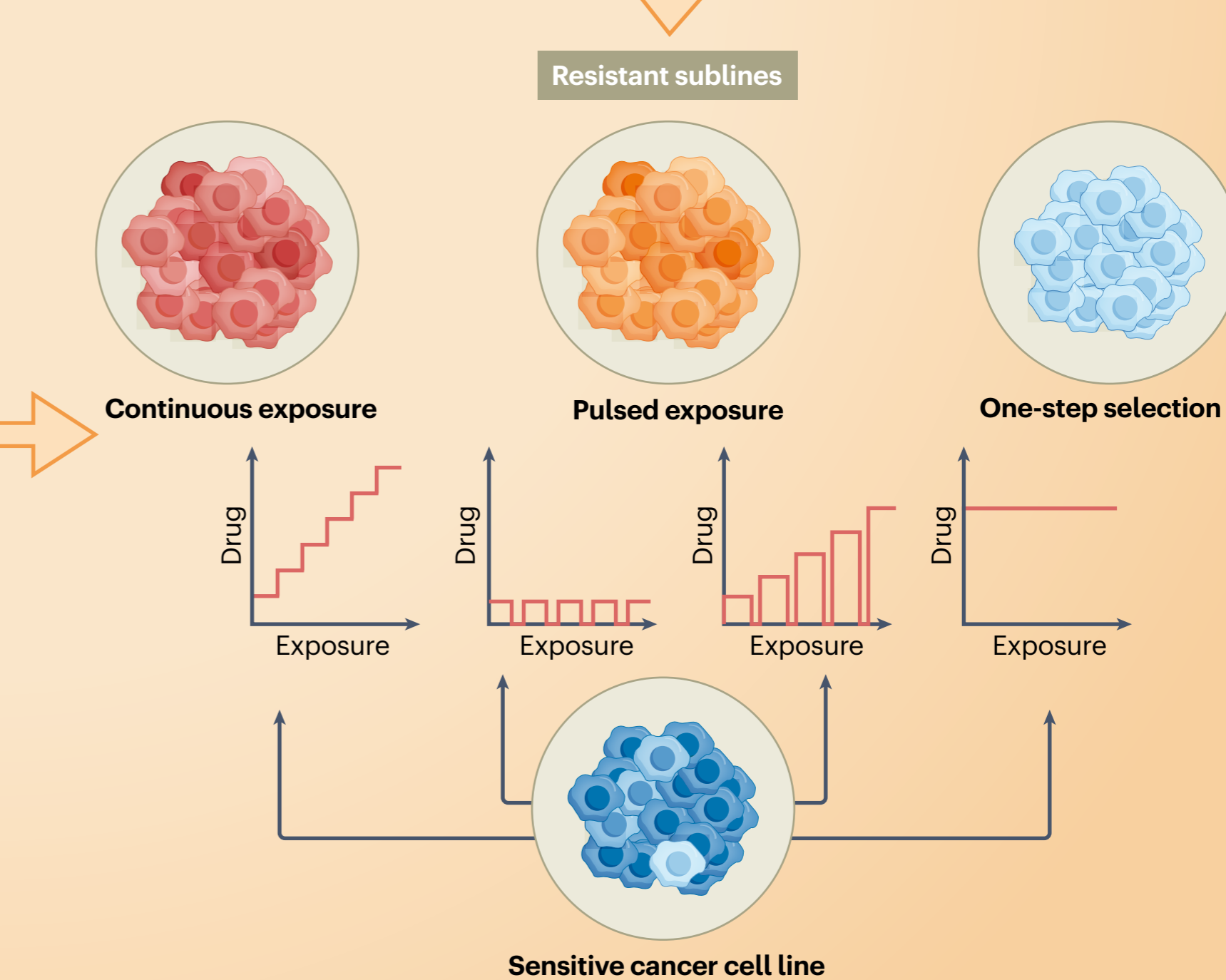
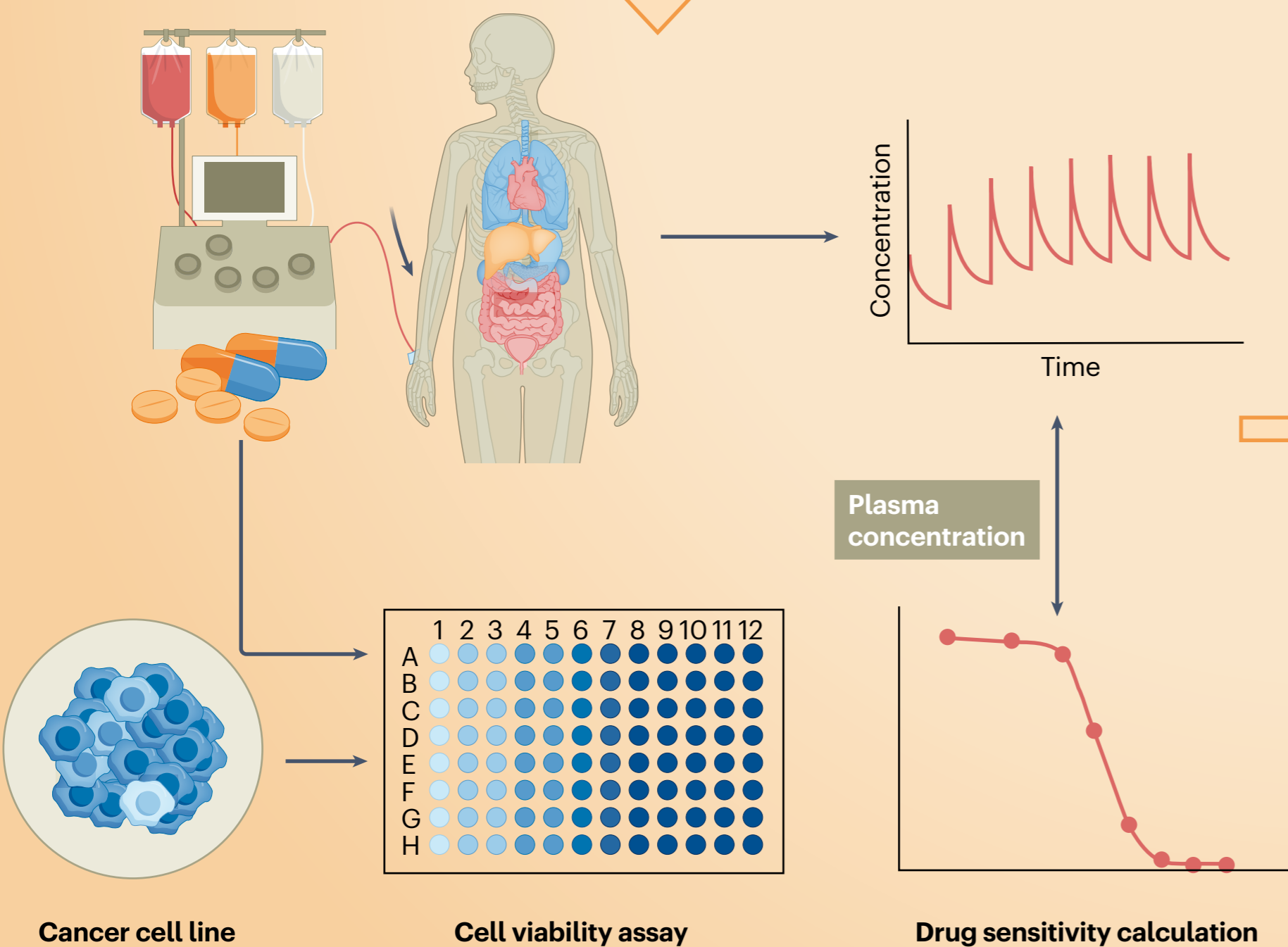
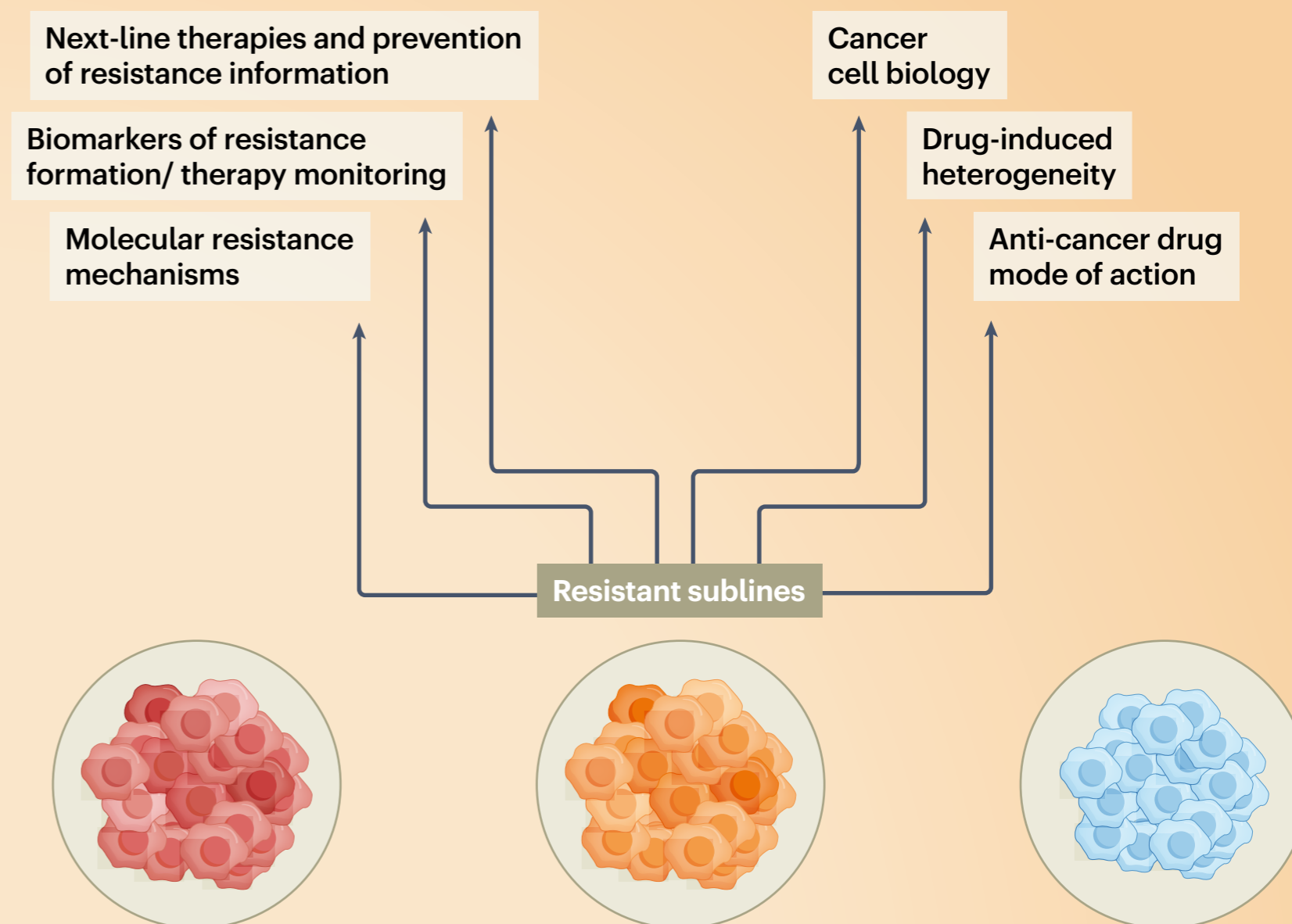
Tumour (biopsy) material or circulating tumour cells (from human patients or animal patients)



## Applications of drug-adapted cancer cell line

Drug adapted cell lines are used to:

- Investigate resistance mechanisms
- Identify biomarkers
- Identify next-line therapies and/or therapies that delay resistance formation
- Investigate the impact of resistance formation on cancer cell biology
- Study drug-induced clonal selection
- Investigate the mode of action of anti-cancer drugs



## Cell line selection for the generation of drug-resistant sublines

If clinical plasma levels are available, it is recommended to select (commercially available) cell lines that are sensitive to clinical drug concentrations for the establishment of acquired resistance models. Three-dimensional model systems (e.g. cancer cell spheroids, cancer cell organoids) are also under investigation.

## Cancer cell line adaptation to anti-cancer drugs

Adaptation to drugs can be induced by continuous cell line exposure to stepwise increasing drug concentrations, pulsed treatments with a fixed dose or increasing doses, or one-step selection of pre-existing resistant subpopulations in a cancer cell line.

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