
LatticeBiologics
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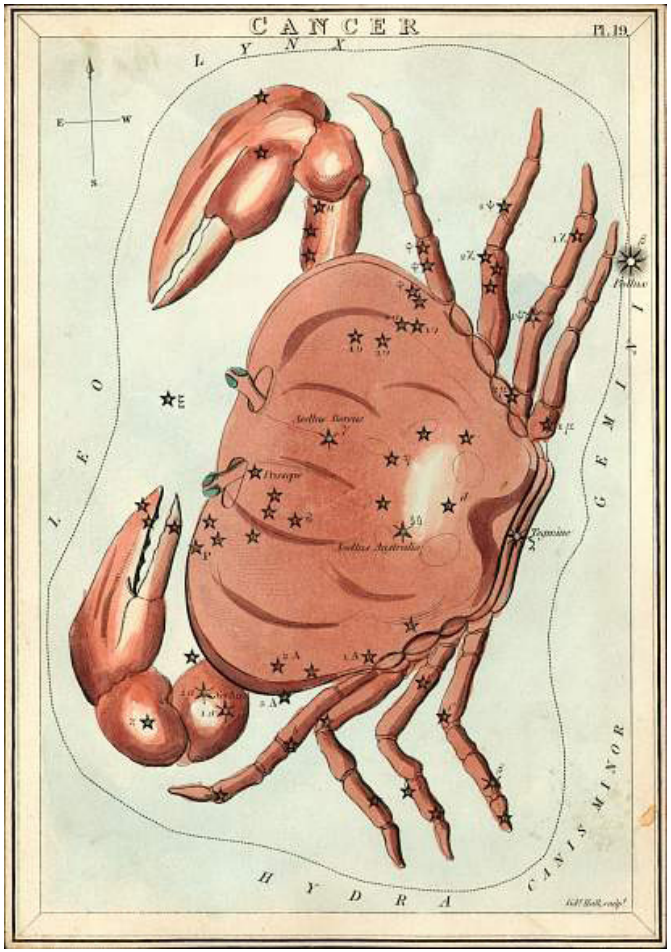
MIRROR IMAGE
The future of cancer diagnostics
may be closer than it appears
Advanced molecular techniques, fluorescence,
and reconstruction of the tumor microenvironment.

The many faces of CANCER

The National Institute of Health's National Cancer Institute defines cancer not as one disease, but as a "collection of related diseases." Cancer can manifest itself in different tissues and cell types, not just one. As such, the disease type depends on the specific kind of cells affected.[1]



What is cancer?

Unlike normal healthy cells, cancer cells are distinguished by their rapid, unrestricted proliferative growth and division. **In other words, their growth is out of control.**

Origins

The term "carcinoma" is derived, in part, from the Greek word *carcinos,* meaning crab or crayfish.

Hippocrates, himself, described cancer this way based on the surface appearance of solid malignant tumors, with "veins stretched on all sides" like a crab's feet.[2]

The suffix "-oma" is Greek for "swelling" and means tumor.

[1] *http://www.cancer.gov/about-cancer/what-is-cancer*
[2] *https://en.wikipedia.org/wiki/History_of_cancer*

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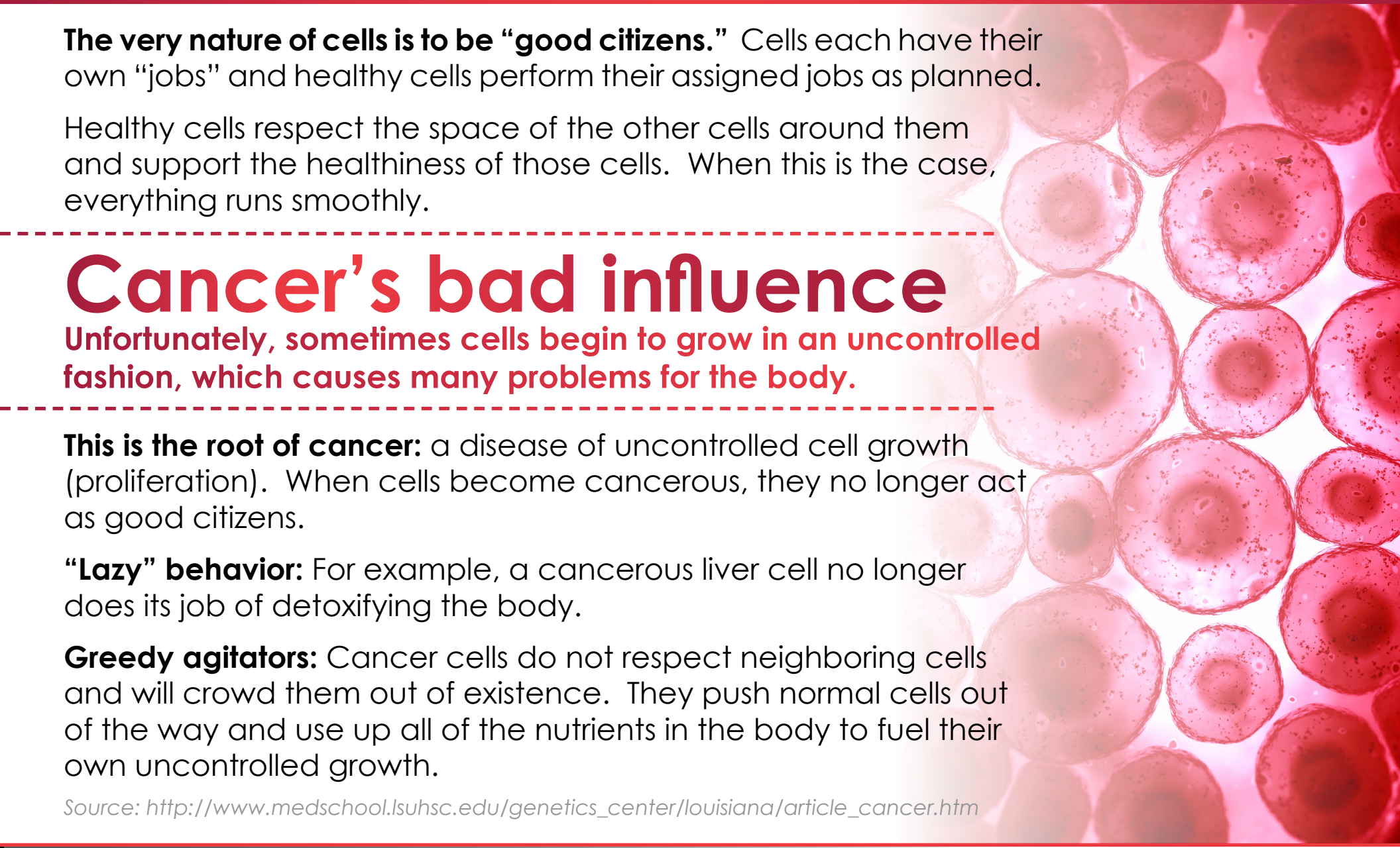
When cells aren't neighborly

The very nature of cells is to be "good citizens." Cells each have their own "jobs" and healthy cells perform their assigned jobs as planned.

Healthy cells respect the space of the other cells around them and support the healthiness of those cells. When this is the case, everything runs smoothly.



Cancer's bad influence

Unfortunately, sometimes cells begin to grow in an uncontrolled fashion, which causes many problems for the body.

This is the root of cancer: a disease of uncontrolled cell growth (proliferation). When cells become cancerous, they no longer act as good citizens.

"Lazy" behavior: For example, a cancerous liver cell no longer does its job of detoxifying the body.

Greedy agitators: Cancer cells do not respect neighboring cells and will crowd them out of existence. They push normal cells out of the way and use up all of the nutrients in the body to fuel their own uncontrolled growth.

Source: http://www.medschool.lsuhsc.edu/genetics_center/louisiana/article_cancer.htm

Cancer diagnostics THEN & NOW

HISTORICAL

Ancient Egypt: The earliest known descriptions of cancer appear in *papyri* written around 1600 B.C. These are believed to date from sources as early as 2500 B.C. They illustrate the first direct knowledge of Egyptian medical practice.

Ancient Greece: It was against Greek tradition to open the body, so early cancer diagnosis was largely empirical and non-invasive (meaning, it relied on the observation of outwardly visible solid tumors with distinct appearances).

For this reason, Hippocrates and others only described and made drawings of outwardly visible tumors on the skin, nose, and breasts.[1]

[2][1]*https://en.wikipedia.org/wiki/History_of_cancer*

MODERN DAY

Beneath the Surface: Cancer encompasses many different diseases, including those that do not give rise to solid tumors (e.g. leukemia). Specific diagnostic tests are necessary to get the full picture.

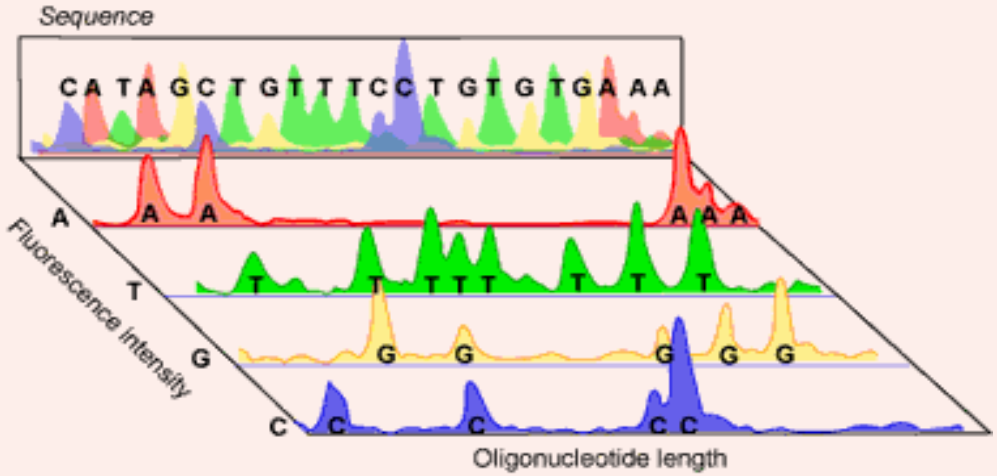
Modern Tools: Advanced cellular imaging techniques empower pathologists and researchers to understand how cancer is manifesting itself at the cellular level.

Today's specialized technologies for analyzing cancer cells include the **use of specialized fluorescent dyes, measurement of gene expression, and advanced optical techniques.** These tools provide a snapshot of otherwise normal cellular processes gone wrong.

Modern cancer diagnostics

Today's cancer diagnostics aim to identify:

- **Where primary tumors are located**
- **If and where cancer has spread throughout the body**
- **The "stage" of the cancer**



Advances in DNA sequencing technologies using automation and fluorescent compounds have made cancer genetics tests a routine part of wellness care.

In addition to initial diagnostic characterization, further tests can inform the best pathways of treatment and may include:

- **Tumor genetics** - DNA sequencing can identify mutations or chromosomal abnormalities that drive the transformation of normal cells into cancerous cells
- **Tumor biomarkers** - Substances shed by the tumor, including proteins or cellular components that can be detected in the blood or other bodily fluids)

Source: http://www.cancer.net/navigating-cancer-care/diagnosing-cancer/stages-cancer
Image Source: http://www.scq.ubc.ca/genome-projects-uncovering-the-blueprints-of-biology/

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Fluorescence as a diagnostic tool

Ground Breakers

Lattice Biologics Scientific Advisory Board (SAB) member, Dr. Danny Enepekides, co-authored a study to investigate the benefits of a special type of fluorescence for diagnosing cancer in oral cells (malignant and premalignant lesions).

STUDY

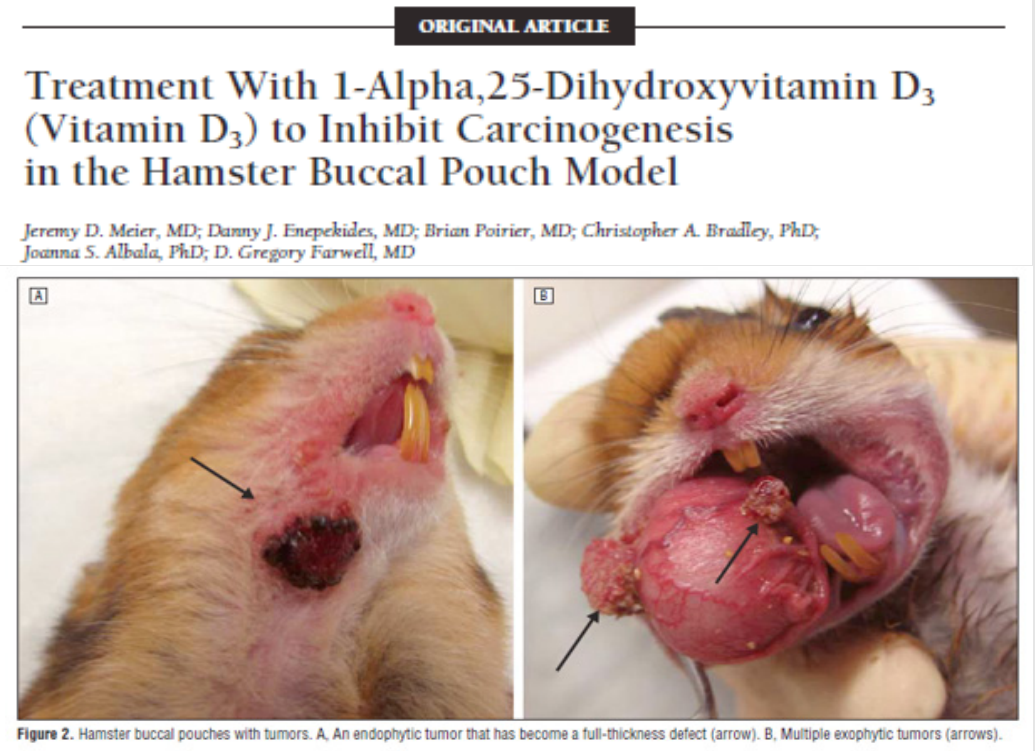
"Time-resolved fluorescence spectroscopy as a diagnostic technique of oral carcinoma: Validation in the hamster buccal pouch model."

Conclusion: The addition of time-resolved fluorescence-derived parameters significantly improved the capability of fluorescence spectroscopy-based diagnostics.

This provides a non-invasive diagnostic technique for head and neck cancer.

Source: Farwell DG, Meier JD, Park J, Sun Y, Coffman H, Poirier B, Phipps J, Tinling S, Enepekides DJ, Marcu L. (2010) "Time-resolved fluorescence spectroscopy as a diagnostic technique of oral carcinoma: Validation in the hamster buccal pouch model." Arch Otolaryngol Head Neck Surg 136: 126-133

Lattice Biologics Product Development Director, Christopher Bradley, PhD co-authored an earlier publication with Dr. Enepekides using the same *hamster buccal pouch* system to demonstrate the merit of pre-administered Vitamin D for cancer-preventative effects.



ORIGINAL ARTICLE

Treatment With 1-Alpha,25-Dihydroxyvitamin D_3 (Vitamin D_3) to Inhibit Carcinogenesis in the Hamster Buccal Pouch Model

Jeremy D. Meier, MD; Danny J. Enepekides, MD; Brian Poirier, MD; Christopher A. Bradley, PhD; Joanna S. Albala, PhD; D. Gregory Farwell, MD

Figure 2. Hamster buccal pouches with tumors. A, An endophytic tumor that has become a full-thickness defect (arrow). B, Multiple exophytic tumors (arrows).

Hamster buccal pouches with tumors

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Cancer's molecular mechanisms

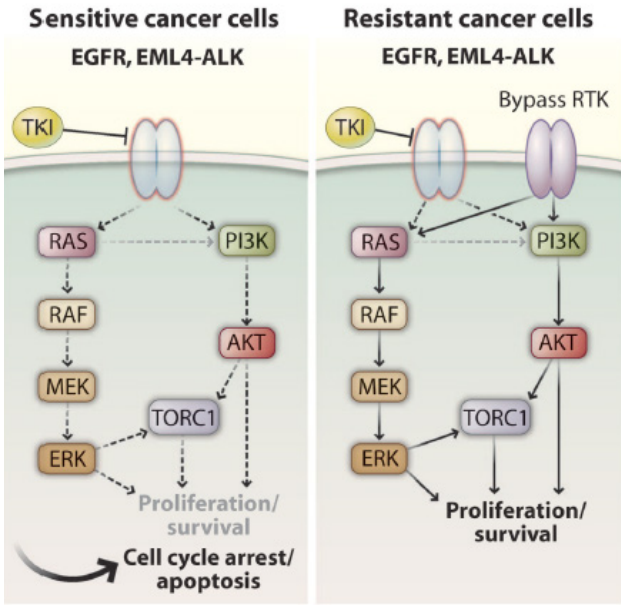
THE MOLECULAR MECHANISMS OF CANCER PROGRESSION

Although the number of drugs available to treat cancers has increased significantly over the years, cancer still often develops a resistance to treatment.

Effective secondary therapies have been developed to combat this by understanding the molecular mechanisms behind each drug resistance and applying modern molecular biology techniques.

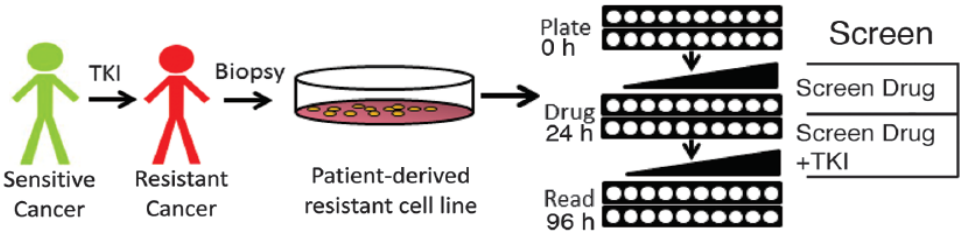
Getting Closer: One of these secondary treatment examples is the treatment of lung cancers using Tyrosine Kinase Inhibitors (TKIs). TKIs target cellular receptors such as EGFR (Endothelial Growth Factor Receptor).

When mutated, EGFR can over-activate the downstream signals that control the rate of cellular growth and division. TKIs dampen this effect, but, sometimes only temporarily, because the cancer cells recruit an alternate cell receptor to flip the switch from "OFF" to "ON" again.



Crystal AS, et al. (2014) Patient derived models of acquired resistance can identify effective drug combinations for cancer. Science 346: 1480-6

Now the challenge is to develop accurate drug screens using the patient's own cells which have been grown in a dish. This requires effectively reproducing the tumor microenvironment. Lattice understands how to use human-derived ECM and optimal growth conditions to mimic the native environment of a biopsy site.



Niederst MJ and Engelman JA (2013) Bypass mechanisms of resistance to receptor tyrosine kinase inhibition in lung cancer. Sci Signal 6(294)

Tumor cells and their surroundings

Cancer cells can influence their surrounding microenvironment, affecting normal cells, molecules, and blood vessels that surround and feed tumors.

One of the critical challenges of growing patient tumor cells in a dish is replicating the actual conditions those cells experienced when they were still growing in the patient's body. Re-establishing those conditions is essential for analyzing the tumor cells' natural behavior and understanding how they would respond to various stimuli or treatments within the body. ***The goal is to create a lab environment that closely mimics the cells' natural environment in order to form accurate conclusions.***

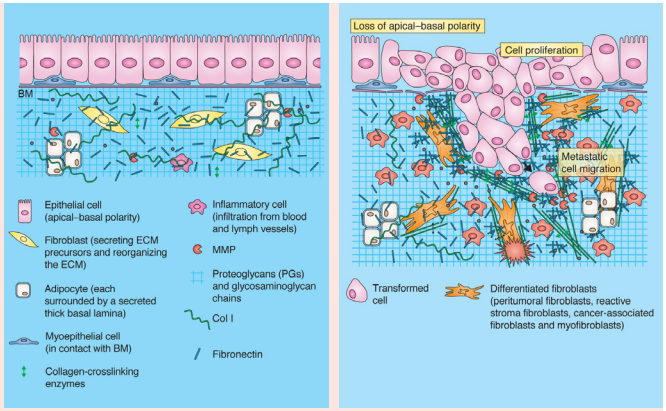
Growth Techniques: There are multiple methods for growing cells within a lab, such as: monolayer (2D) culture, 3D culture, and suspension.

Trouble with the "Dish Life": Cells can respond differently to drugs administered to them, depending on the way they are grown.[1]

In some cases, they will behave like stem cells, showing the ability to self-renew. Other times, they may go dormant. These different cellular behaviors are related to the microenvironment the cells experience when grown in a dish and may not accurately reflect what the experience of the cells would be if they were still in the patient's body.

[1] *Bernardo MM, et al (2015) Maspin expression in prostate tumor cells averts stemness and stratifies drug sensitivity. Cancer Res 75: 3970-3979*

Extracellular Matrix (ECM) Structure and Function



Normal Condition Tumor Condition

Growth Method Examples

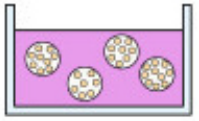
2D Culture

Monolayer culture

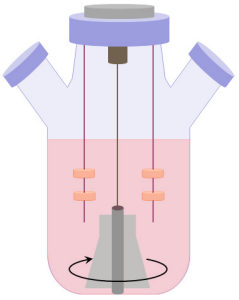
CD Culture

Pellet culture

Alginate beads



Suspension



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Building the Microenvironment

Lattice Biologics will be developing products that promote the ability of patients' own stem cells to:

- **Migrate** to the site of injury
- **Engraft** (implant)
- **Proliferate** (multiply)
- **Vascularize** (form blood vessels)
- **Heal** the injury

This technology is based on customizing the Extracellular Matrix (ECM) to mimic the optimal microenvironment for cell growth and division.

New Life for Cancer Diagnostics:
In addition to their therapeutic abilities for improved healing, these technologies could also support the development of advanced cancer diagnostics tools. By replicating the microenvironment tumor cells experience in the body, we can achieve more accurate results when testing drugs in a dish (lab setting).

This next generation of cancer diagnostics will better inform anti-cancer therapies customized for individual patient results.

In this case... IMITATION **is the highest form of** INNOVATION

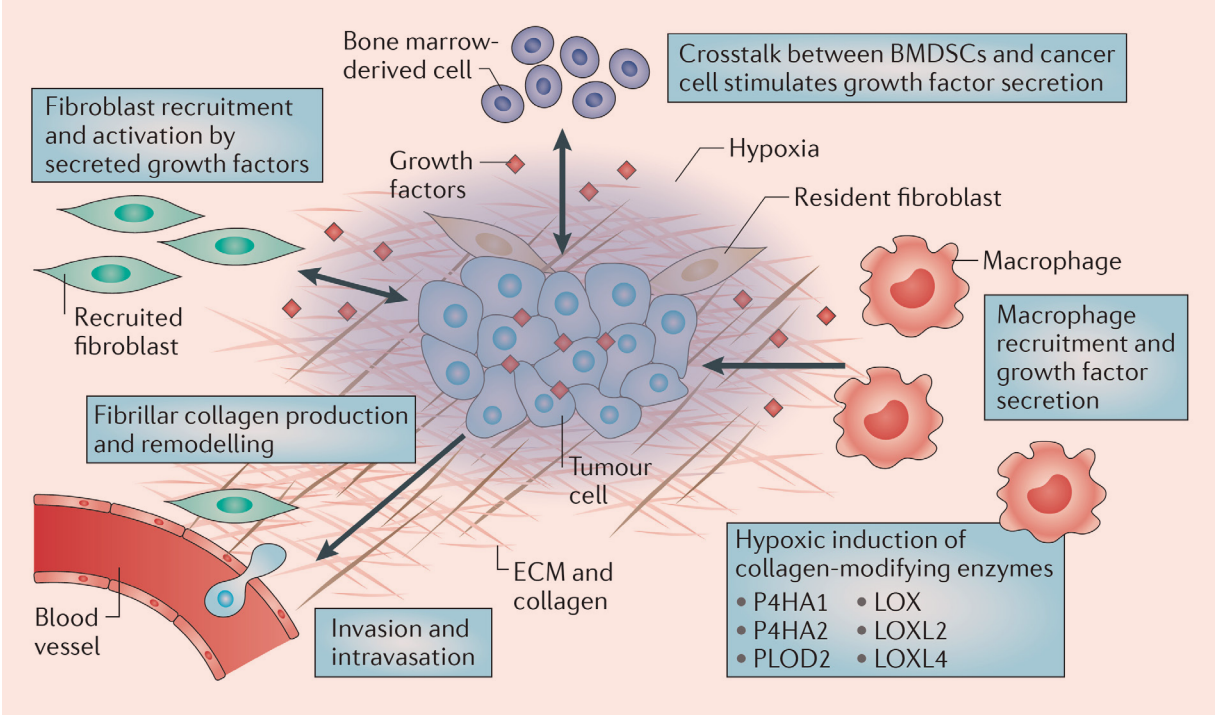

Image: Gilkes DM, Semenza GL, Wirtz D (2014) "Hypoxia and the extracellular matrix: drivers of tumour metastasis." Nature Reviews Cancer 14, 430–439