BIOCEV Biotechnology and Biomedicine Centre of the Academy of Sciences and Charles University in Vestec

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Migrastatics: Redirecting R&D in Solid Cancer Towards Metastasis?

Prof. Jan Brábek, PhD.

Cell Invasion in Cancer Laboratory

Charles University, Faculty of Science
Department of Cell Biology and BIOCEV

Member of THE INVADOSOME CONSORTIUM

In 2020, the problems with solid cancer are: ***ineffective, not safe enough, and unaffordable medicines!***

Do cancer drugs improve survival or quality of life?

You don't need to know, according to our broken regulatory system

Vinay Prasad

- between 2008 and 2013 both FDA and EMA mostly approved cancer drugs without evidence of prolonged survival or improved quality of life
- less than 15% were shown later to improve survival
- **the median improvement in survival among patients treated with 71 novel drugs for solid cancer was just 9 weeks!**

In 2020, the problems with solid cancer are: ***ineffective, not safe enough, and unaffordable medicines!***

JAMA Oncology

Estimation of the Percentage of US Patients With Cancer Who Benefit From Genome-Driven Oncology

John Marquart, BA; Emerson Y. Chen, MD; Vinay Prasad, MD, MPH

Question How many US patients with cancer benefit from genome-targeted therapies?

Findings

- **in 2006 - 5% of patients were eligible, in 2018 - 8%**
- **In 2006 - less than 1% of patients responded, in 2018 - 5%**

In 2020, the problems with solid cancer are: ***ineffective, not safe enough, and unaffordable medicines!***

Cancer, checkpoint inhibitors, and confusion.

THE LANCET Oncology

Fernandes M, Brábek J.
Lancet Oncol. 2017 18(11):e632.

In many cases great improvement of treatment efficiency, but compared to chemotherapy, serious adverse effects are currently difficult to predict.

JAMA Insights | CLINICAL UPDATE

Immune Checkpoint Inhibitor Toxicity in 2018

Douglas B. Johnson, MD; Sunandana Chandra, MD; Jeffrey A. Sosman, MD

In 2020, the problems with solid cancer are: ***ineffective, not safe enough, and unaffordable medicines!***

Affordable cancer care.

Fernandes M, Brábek J.
Lancet Oncol. 2012 13(1):e2-3.

THE LANCET Oncology

Affordable cancer care: pipedream or achievable reality?

Collingridge D, Sullivan R.
Lancet Oncol. 2014 15(3):257-8.

Continuing failure despite:

- excellent scientists
- advanced technology
- generous funding

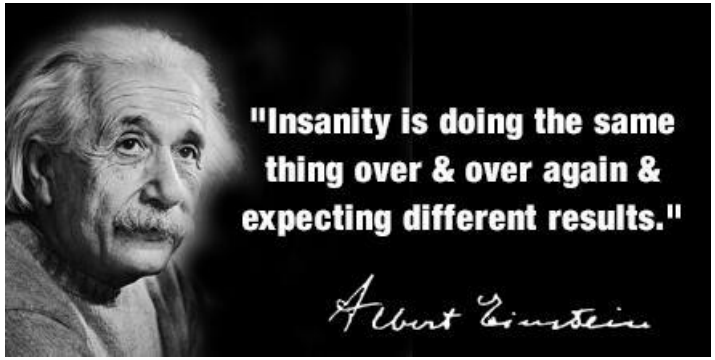
WHY?

Not focused on central issue:
Invasion and metastasis!

In contrast to hematopoetic malignancies, **solid cancer is predominantly a disease of invasion and metastasis**, not an uncontrolled proliferation!

x

Pharma companies don't concentrate on solving the problem of metastasis (the thing that kills people); they mostly focus on devising drugs that shrink tumors (the things that don't).

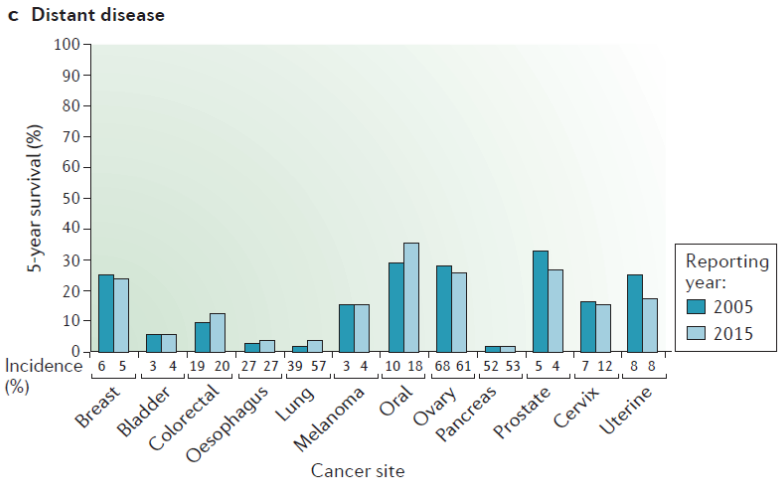


In solid cancer, does ongoing metastatic activity negate the "benefit" of tumor shrinkage?

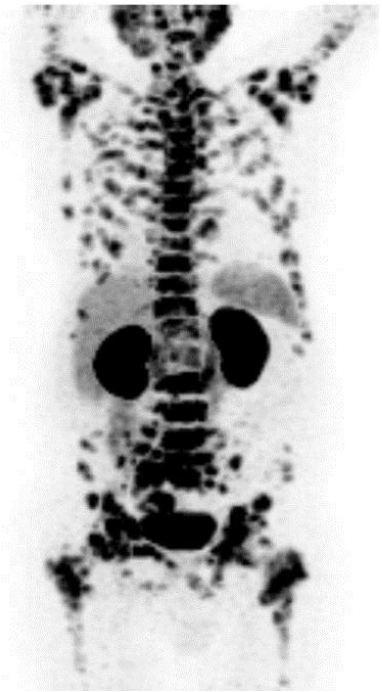
YES!

METASTASES

- **metastases** responsible for **90 % of deaths in cancer patients**



(Steeg, 2016)



METASTASES

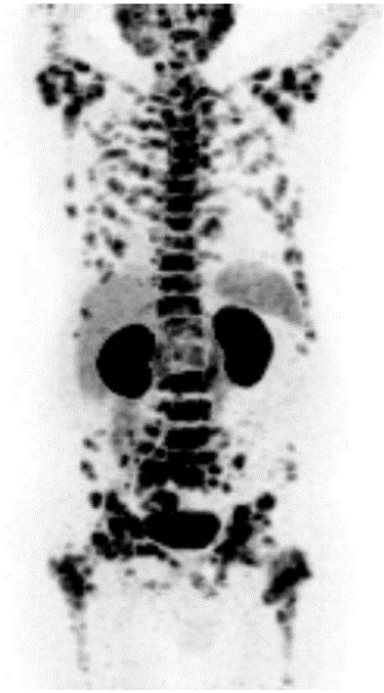
- **invasion and metastasis - the only real cancer hallmark**

  (prof. Y. Lazebnik)

- understanding the mechanisms of invasion and metastasis **critical for the development of effective anti-cancer treatment**

- change in regulations required - **criteria of effectiveness for antimetastatic drugs**

  (Brábek and Fernandes, The Lancet Oncology, 2012)



METASTATIC CASCADE

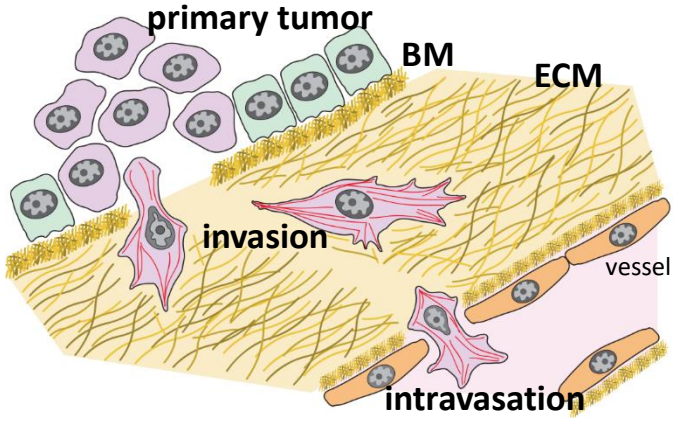
I. Invasion – from primary tumor into the surrounding tissue.

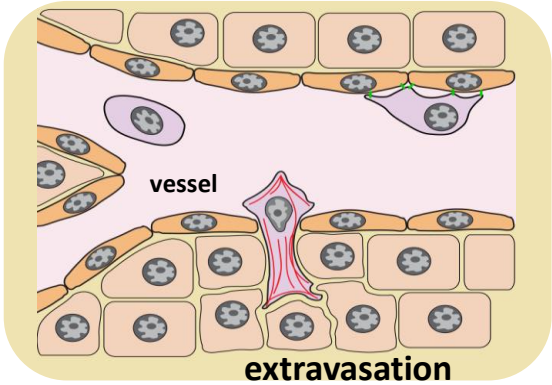
II. Intravasation into blood or lymphatic vessel.

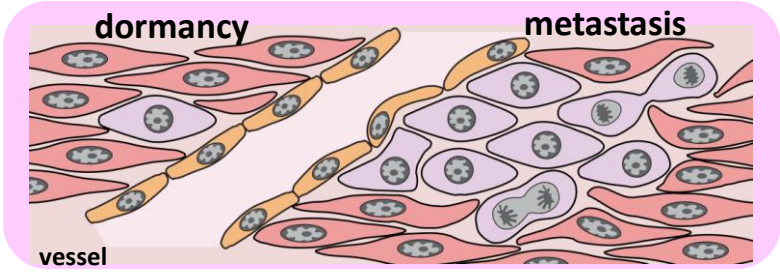
III. Transport to the secondary site and survival in the bloodstream.

IV. Extravasation at the secondary site.

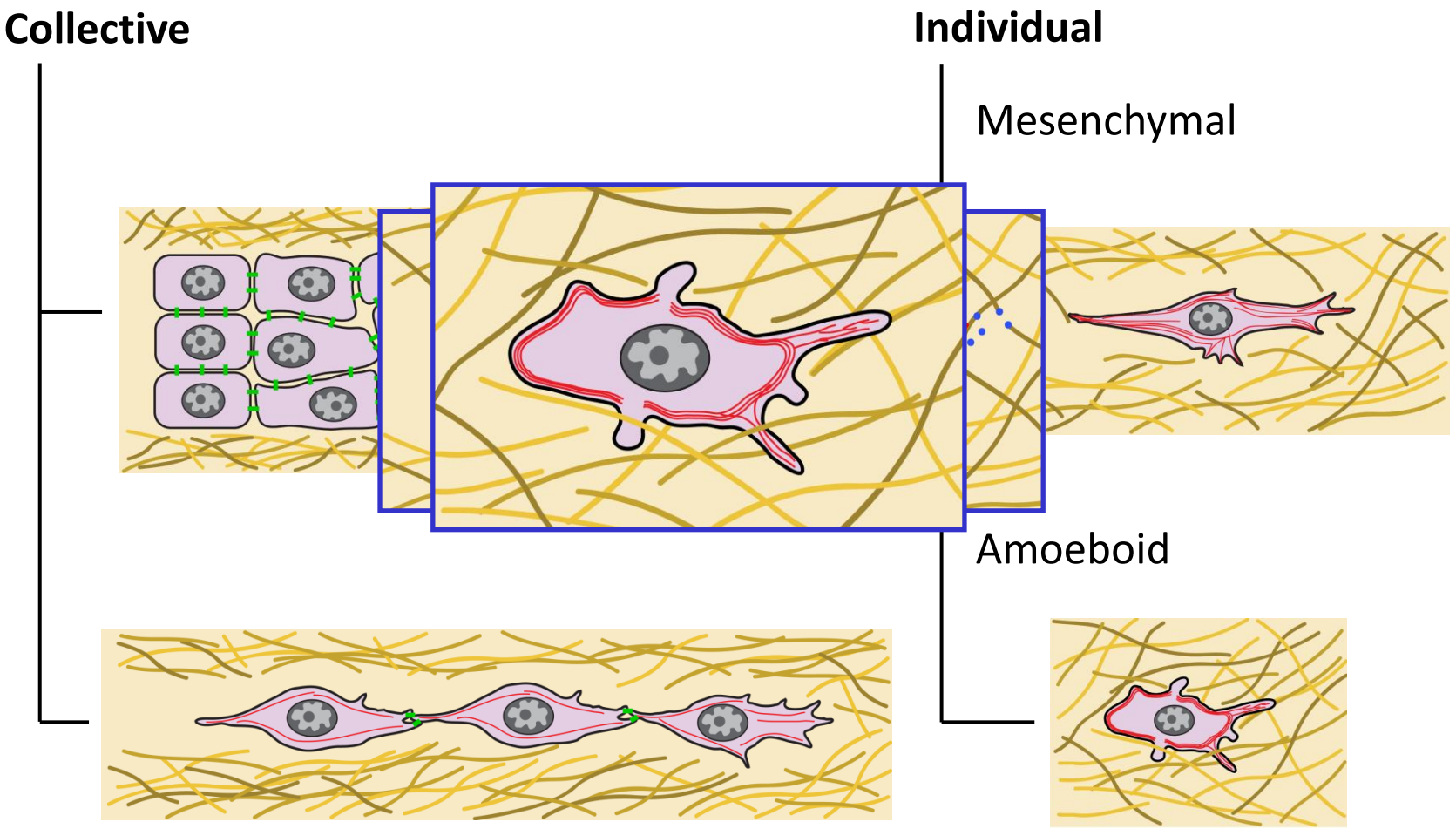
V. Proliferation at the secondary site, formation of metastases.





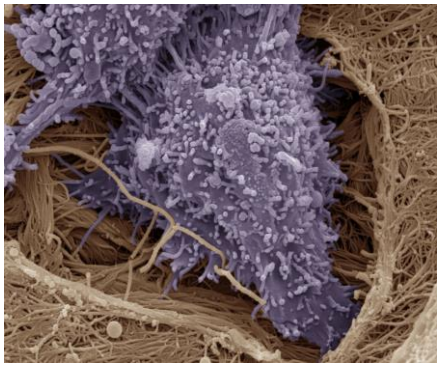


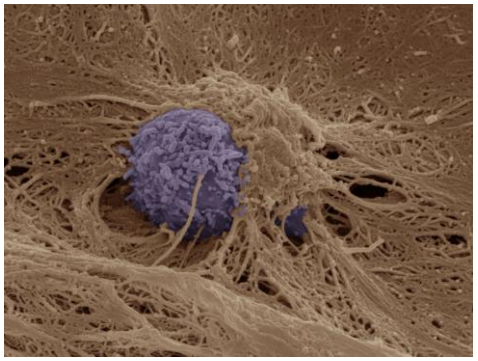
MODES OF CANCER CELL INVASIVENESS

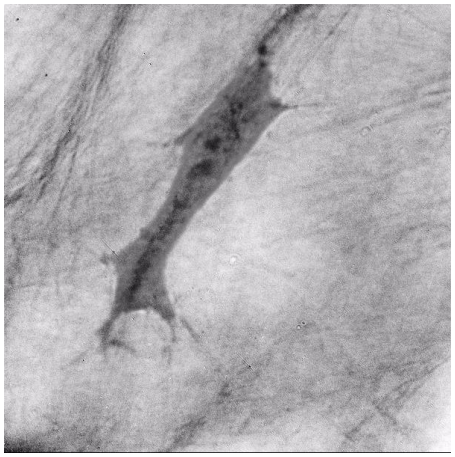


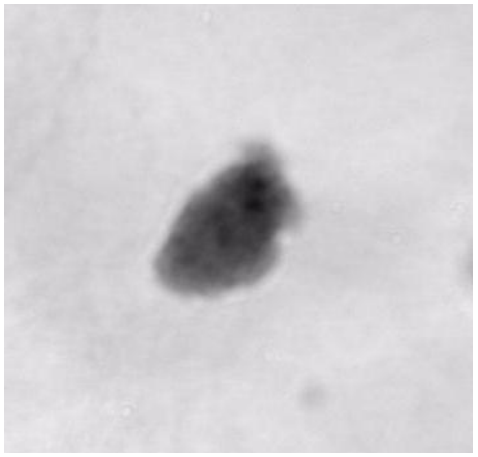
MESENCHYMAL AND AMOEBOID INVASIVENESS

	Mesenchymal	Amoeboid
Morphology	Elongated with protrusions at the leading edge	Rounded with membrane blebs
Adhesion to the ECM	Strong, numerous FA	Weak, integrin-independent
Force generation	Cell-ECM adhesion and protrusive activity at the leading edge	Enhanced cell contractility due to actomyosin cortex
Speed	0,1 -1 μm/min	Up to 15 μm/min
Rate limiting step	Proteolysis of the ECM, FA turnover	Nuclear deformability
Activated GTPase	Rac1	RhoA



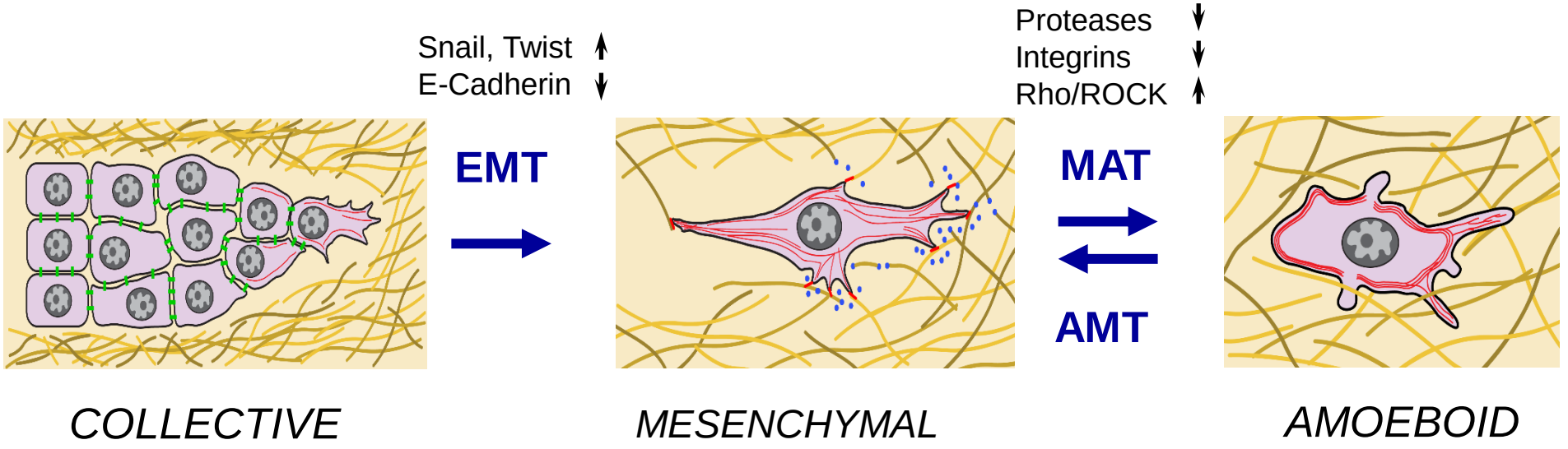






CANCER CELL INVASION PLASTICITY

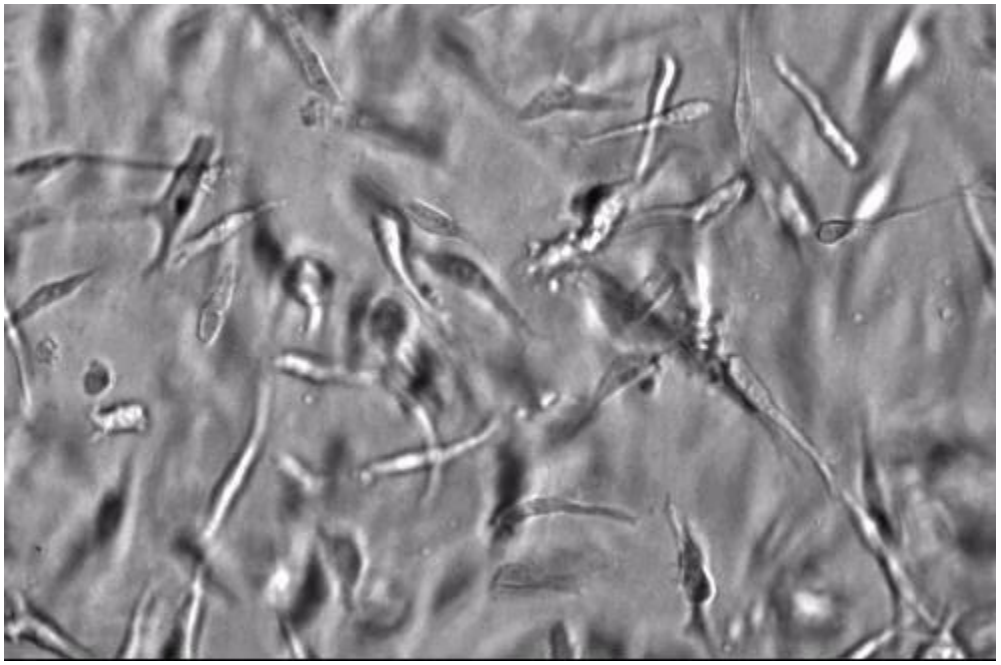
EMT : Epithelio-mesenchymal transition
MAT : Mesenchymal-ameboid transition
AMT : Amoeboid-mesenchymal transition



- AMT/MAT represents an escape mechanism for cancer cell from treatment e.g. with protease inhibitors

MESENCHYMAL TO AMOEBOID TRANSITION

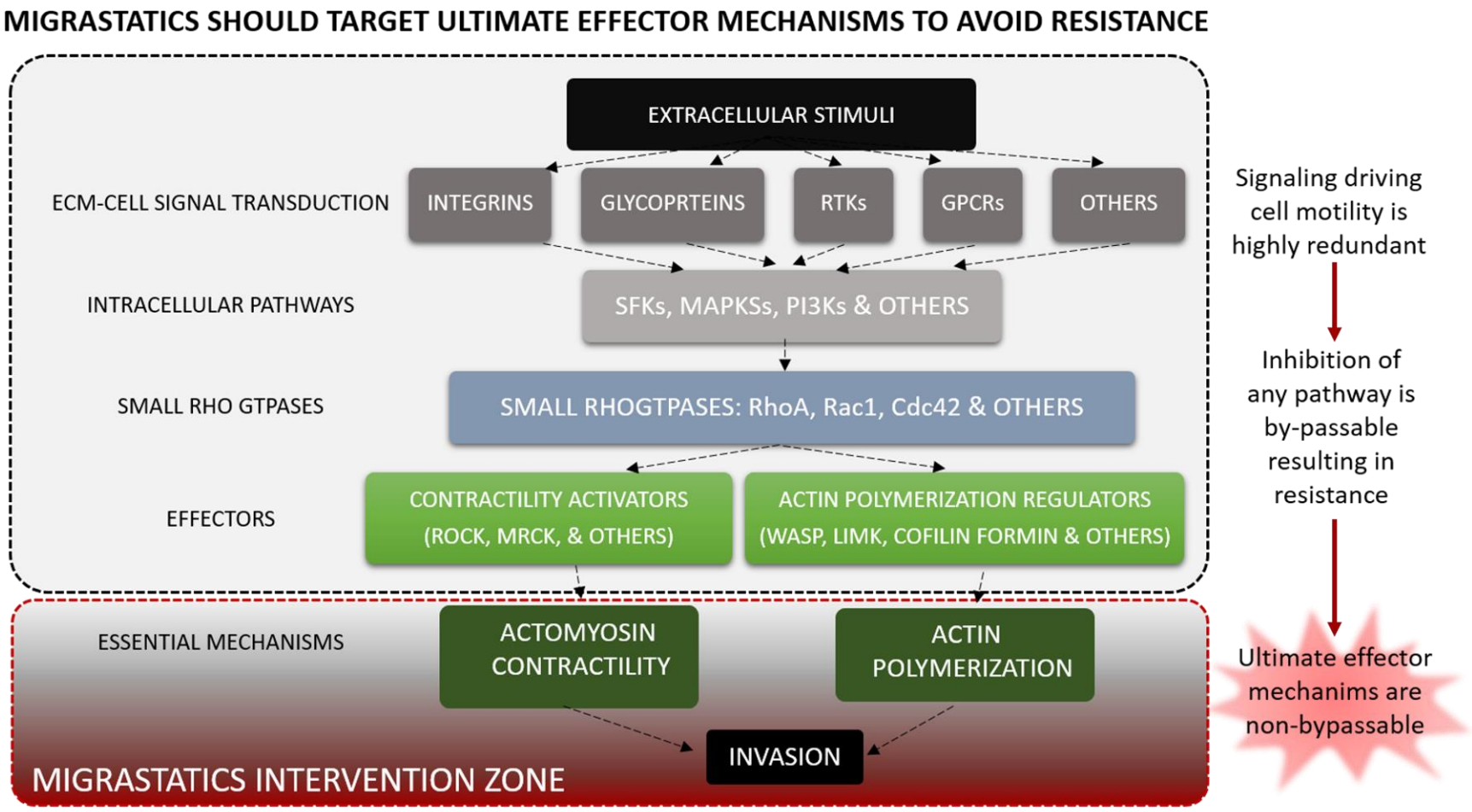
HT1080-iRhoA (G14V)



(Tolde et al., 2018)

Would not be great to have drugs interfering with all modes of cancer cell invasiveness?

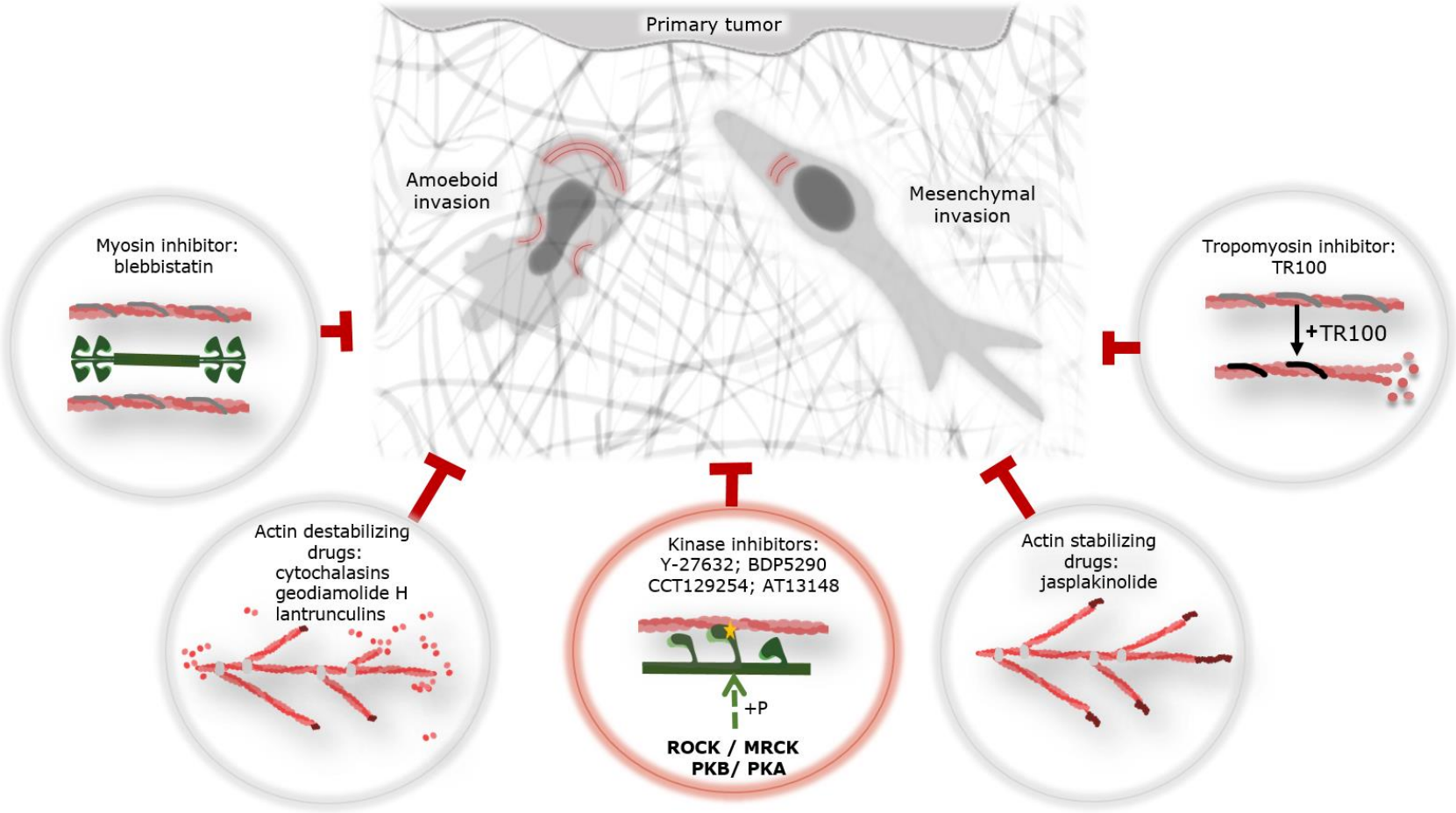
MIGRASTATICS – NEW CATEGORY OF ANTI-CANCER DRUGS



(Gandalovičová et al., 2017)

Trends in Cancer

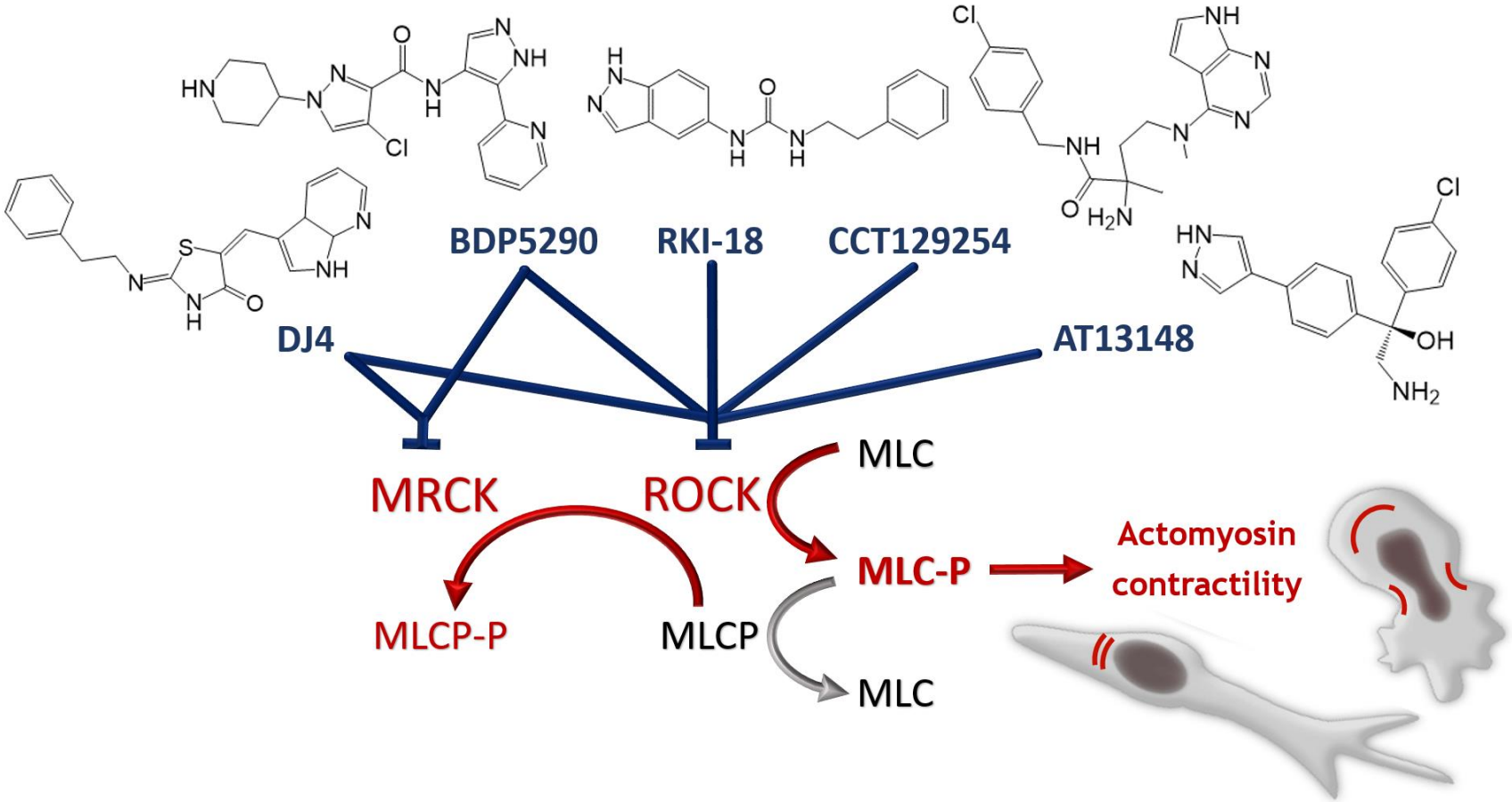
MIGRASTATICS – NEW CATEGORY OF ANTI-CANCER DRUGS



(Gandalovičová et al., 2017)

Trends in Cancer

MIGRASTATICS – NEW CATEGORY OF ANTI-CANCER DRUGS



(Gandalovičová et al., 2017)

MIGRASTATICS – NEW CATEGORY OF ANTI-CANCER DRUGS

ways to target cancer cell migration:

- **mechanistic interference with downstream non-redundant final effector mechanisms of cancer cell migration (actin dynamics, actomyosin contractility)**
- **combined inhibition of protease-dependent and protease-independent invasiveness (e.g. MMP inhibitors + ROCK/MRCK inhibitors)**
- **blocking pro-migratory/pro-invasive signals from cancer microenvironment (e.g. cytokine/chemokine inhibitors, integrin/CD44 inhibitors)**
- **targeting elevated metabolism to inhibit cancer cell migration (e.g. mitochondrially targeted cancer drugs)**
- **preventing cancer cell migration by transdifferentiating of plastic invasive cancer cells into another cell types -e.g. fat cells (Ishay-Ronen et al., Cancer Cell, 2019)**

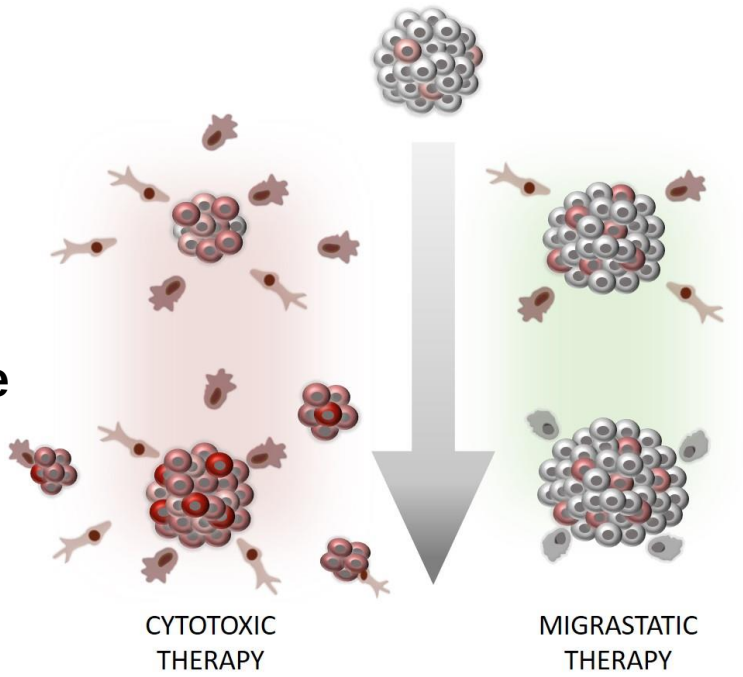
THE CONCEPTUAL ADVANTAGES OF MIGRASTATIC TREATMENT

cytotoxic challenge

darwinian selection of resistant clones

proliferative advantage

invasion/metastasis

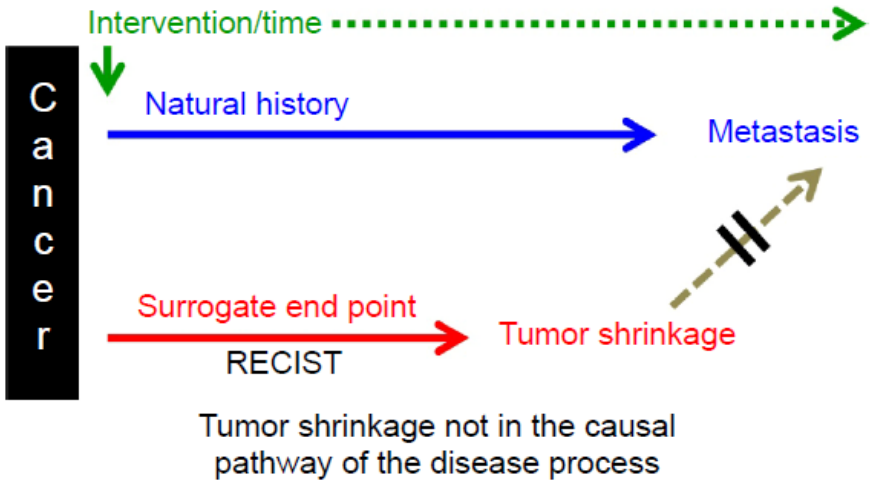


no cytotoxic challenge

rare *resistants without proliferative advantage*

NO invasion/metastasis

ANTIMETASTATIC TREATMENT– PROBLEMS WITH CRITERIA OF EFFECTIVENESS



(Brábek et al., 2016)

BANX

"I'M A BIT WORRIED ABOUT MY REGULATORY ALIGNMENT."

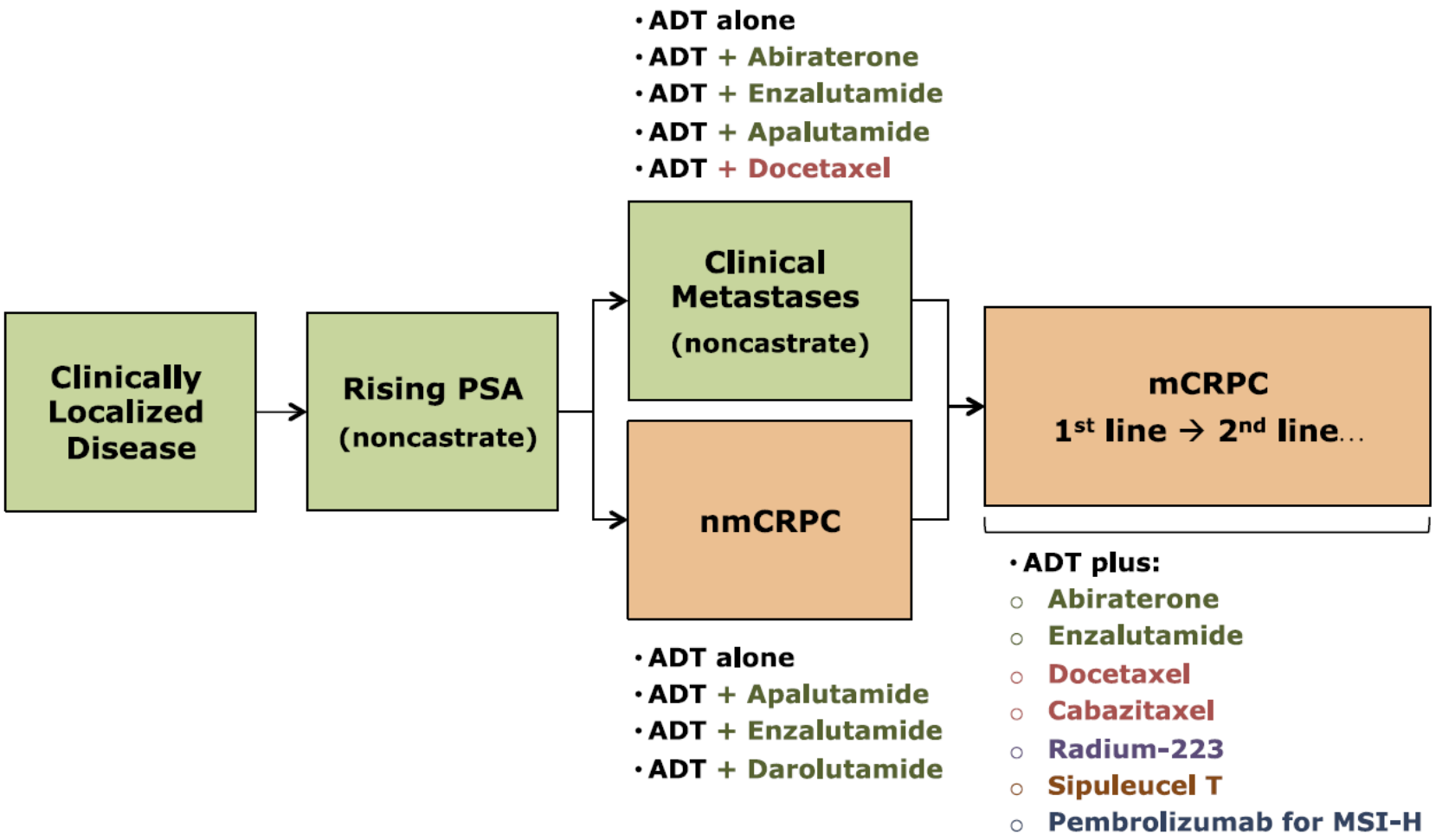


Figure 1 Prostate cancer clinical states model.

Notes: Data created to include the corresponding agents that are FDA approved in each state. Data from Scher et al.[35] Green boxes refer to the castration-sensitive state whereas the orange boxes refer to castration-resistant state. Green texts refer to castration-sensitive state whereas orange texts refer to castration-resistant state.

Abbreviations: ADT, androgen deprivation therapy; nmCRPC, non-metastatic castration-resistant prostate cancer; mCRPC, metastatic castration-resistant prostate cancer; MSI-H, microsatellite instability.

(Bastos and Antonarakis, 2019)

FDA approves new treatment for a certain type of prostate cancer using novel clinical trial endpoint

February 14, 2018

The U.S. FDA today approved Erleada (apalutamide) for the treatment of patients with prostate cancer that has not spread, but that continues to grow despite treatment with hormone therapy. …**This approval is the first to use the endpoint of metastasis-free survival**, measuring the length of time that tumors did not spread to other parts of the body or that death occurred after starting treatment," said Richard Pazdur, M.D., director of the FDA's Oncology Center of Excellence and acting director of the Office of Hematology and Oncology Products in the FDA's Center for Drug Evaluation and Research.

"The FDA had now recognized that a prolonged delay in the development of metastatic disease is an objective and clinically relevant measure," Beaver and colleagues write.

Fernandes M, Rosel D., Brábek J. (2019)
Solid cancer: the new tumor spread endpoint opens novel opportunit
BJC, Invited Editorial, 121(7):513-514

BJC

CONCLUSION:
PLAN B FOR CANCER MOONSHOT INITIATIVE

Plan A Precision medicine (”driver genes” etc.)

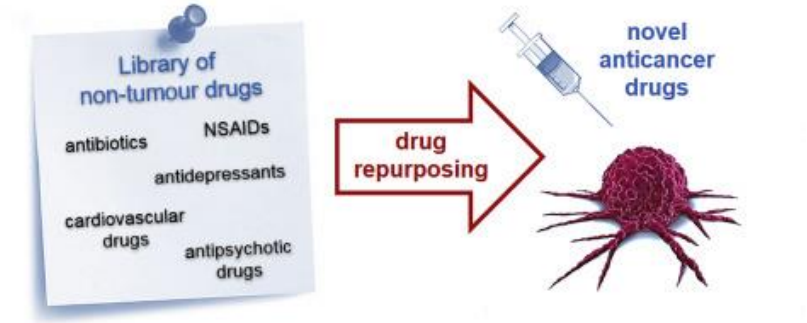
Plan B Therapy directed to ”3 Ms”

cancer microenvironment, motility (MIGRASTATICS) and metabolism

(Brábek, Rosel, Fernandes, New England Journal of Medicine, 2017)

HOW TO ACCELERATE THE AVAILABILITY OF MIGRASTATIC TREATMENT TO CANCER PATIENTS?

DRUG REPURPOSING!



(Antoszczak et al., 2019)

WE STARTED TO ANALYZE ALL FDA-APPROVED DRUGS FOR MIGRASTATIC POTENTIAL

WHAT´S NEXT

- Based on our work, we plan on **exploring the determinants of metastasis and tractable targets for pharma intervention, e.g. migrastatics.**

- Collaboration with medicinal chemists is crucial and we need to explore both synthetic compounds and natural products.

- Accordingly, we plan on making suggestions for the revision of regulations on new cancer drugs. Primarily, rationalizing and justifying criteria for the evaluation of sustainable efficacy.

- **Call on collaboration with clinical oncologists on experimental trials with migrastatics compounds!**

Trends in Cancer

Science & Society

Migrastatics: Redirecting R&D in Solid Cancer Towards Metastasis?

Daniel Rosel,[1]
Michael Fernandes,[2]
Victoria Sanz-Moreno,[3]
and Jan Brábek[1,*]

The concept of 'migrastatics' allows the development of a new drug class that is neither cytotoxic nor antiproliferative but is solely directed towards inhibition of cancer cell motility. Given that the regulatory pathway is open, and migrastatic candidates have been described, it is the right time to enter a new era of antimetastatic treatment.

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