

The role of Mesenchymal Cells in Cholangiocarcinoma

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Department of Cancer Biology

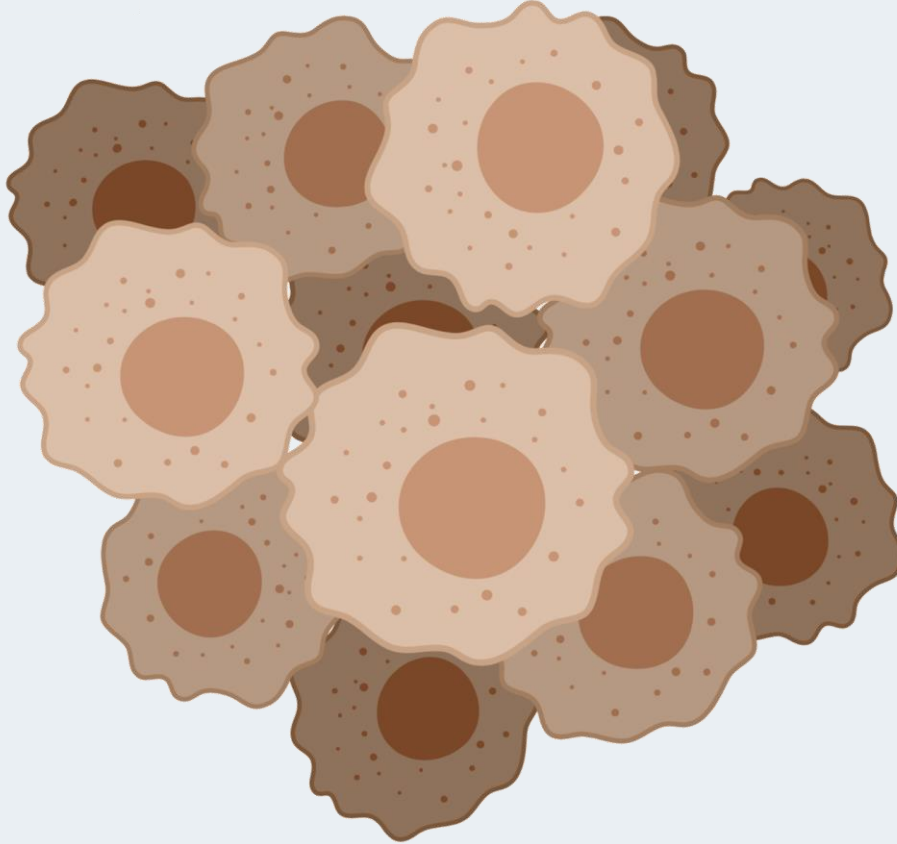
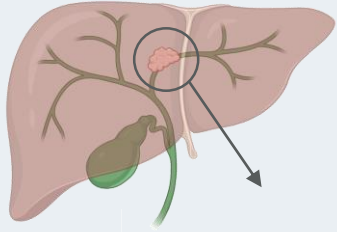
Division of Cancer and Stem Cells

School of Medicine

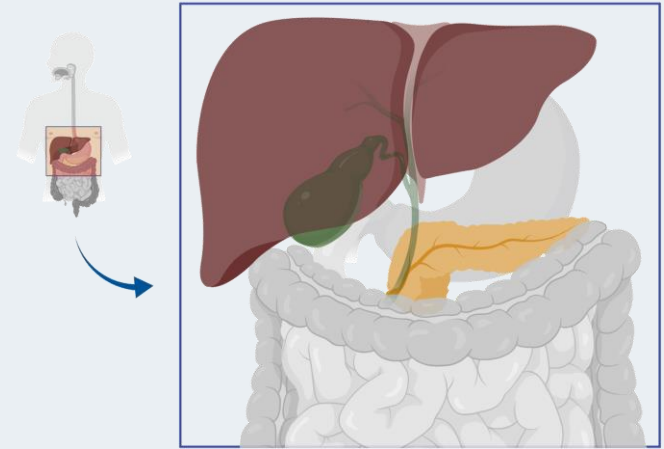
University of Nottingham Biodiscovery Institute

Supervised by Professor Anna M Grabowska and Professor David O Bates

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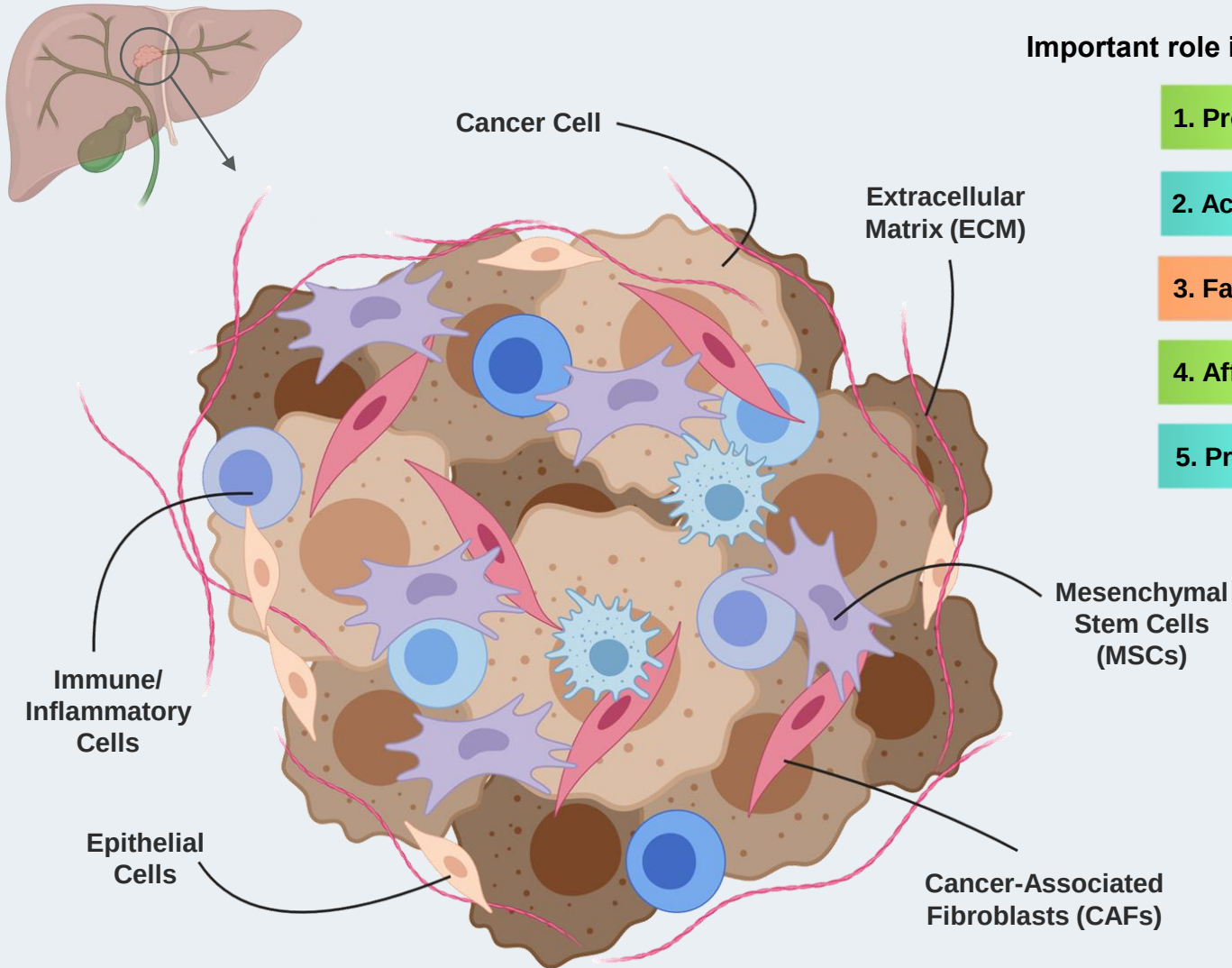
Cholangiocarcinoma



“Cholangiocarcinoma is an epithelial malignancy originating from cholangiocytes”

(Blechacz, 2017)

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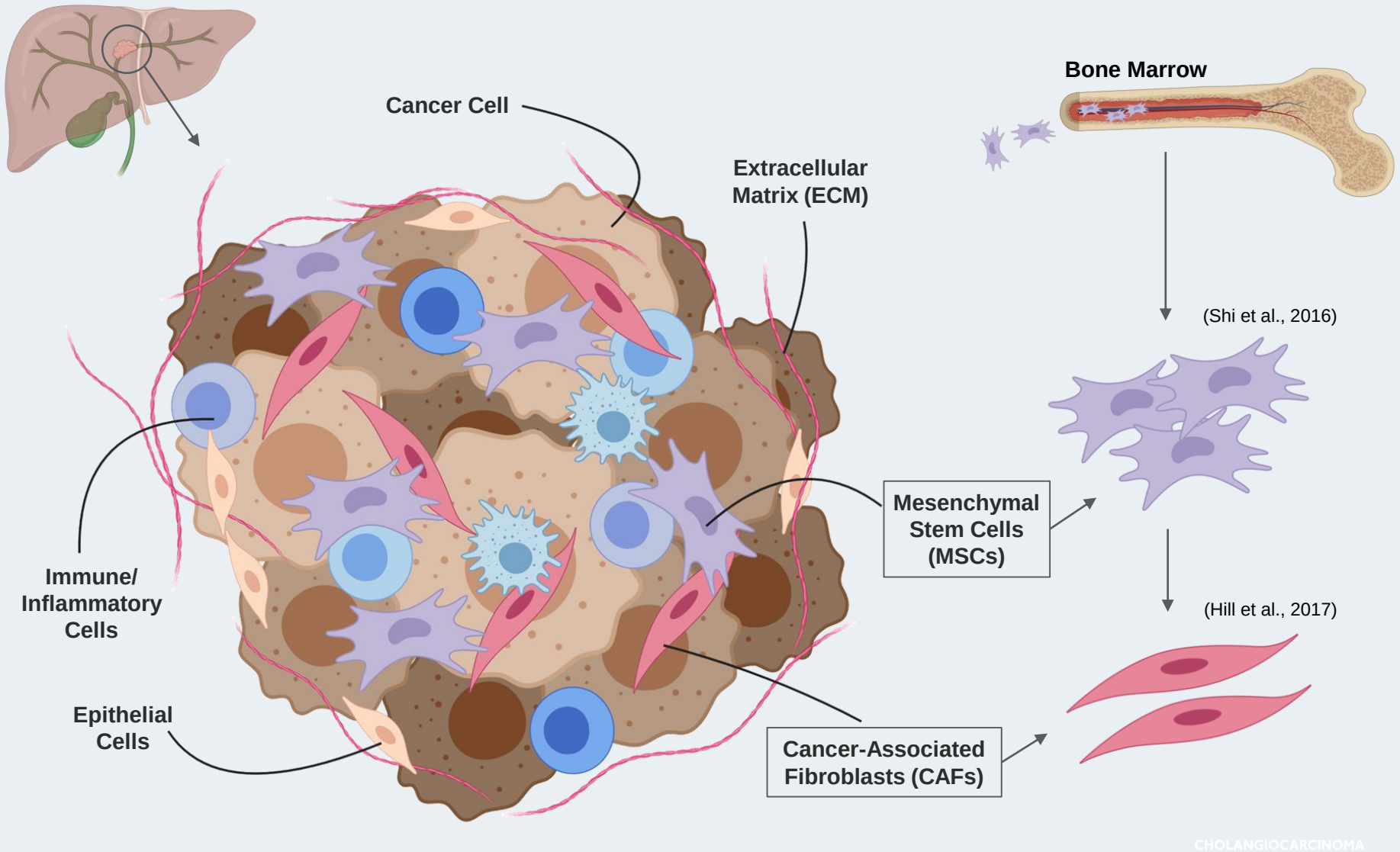


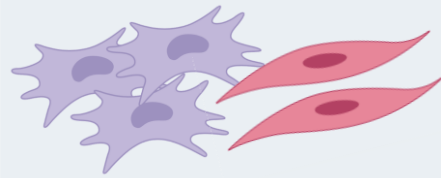
Important role in...

(Chen *et al.*, 2019)

1. Promoting tumour proliferation
2. Accelerating neovascularization
3. Facilitating tumour invasion
4. Affecting immune reactions
5. Preventing apoptosis

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MSCs/CAFs

(Gentilini et al., 2018)

Tumour growth

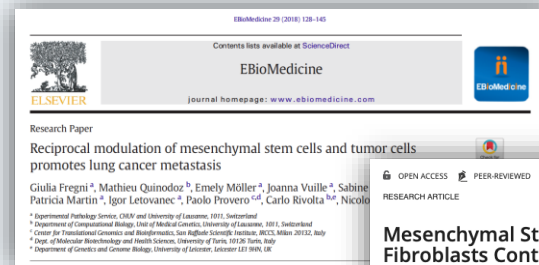
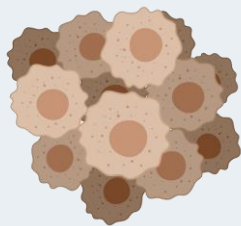
Angiogenesis

Tumour metastasis

Tumour resistance

Immune-suppression

Cancer Cells



Research Paper

Reciprocal modulation of mesenchymal stem cells and tumor cells promotes lung cancer metastasis

Giulia Fregni^a, Mathieu Quinodoz^b, Emely Möller^a, Joanna Vuille^a, Sabine Patricia Martin^a, Igor Letovanec^a, Paolo Provero^{c,d}, Carlo Rivolta^{b,e}, NicolaOPEN ACCESS
PEER-REVIEWED
RESEARCH ARTICLE

Mesenchymal Stem Cell Transition to Tumor-Associated Fibroblasts Contributes to Fibrovascular Network Expansion and Tumor Progression

Erika L. Spaeth¹, Jennifer L. Dembinski², A. Kate Sasser, Keri Watson, Ann Klopp, Brett Hall, Michael Andreeff, Frank Marini³Liang et al. Cell Death and Disease (2019) 10:375
https://doi.org/10.1038/s41419-019-1581-6

Cell Death & Disease

ARTICLE

Open Access

Cancer-associated fibroblasts promote cisplatin resistance in bladder cancer cells by increasing IGF-1/ERβ/Bcl-2 signalling

Xingbo Long^{1,2}, Wei Xiong¹, Xiting Zeng¹, Lin Qi¹, Yi Cai¹, Miao Mo¹, Huichuan Jiang¹, Bisong Zhu¹, Zhi Chen¹ and Yuan Li¹

Received: 9 May 2017

www.impactjournals.com/oncotarget/

Oncotarget, Vol. 7, No. 15

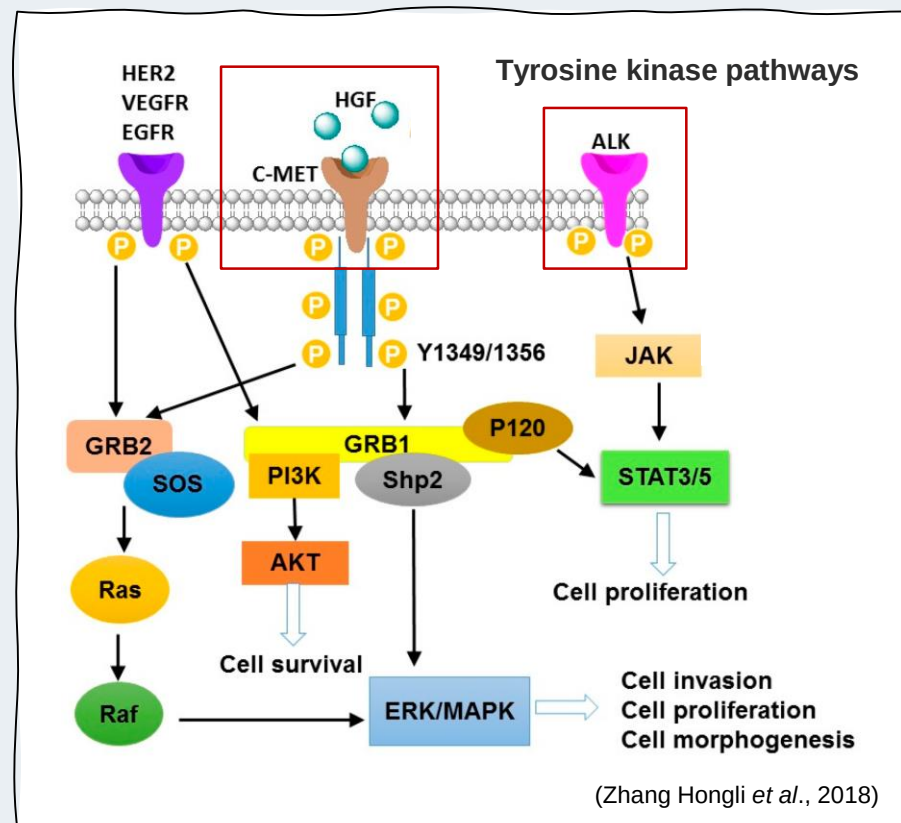
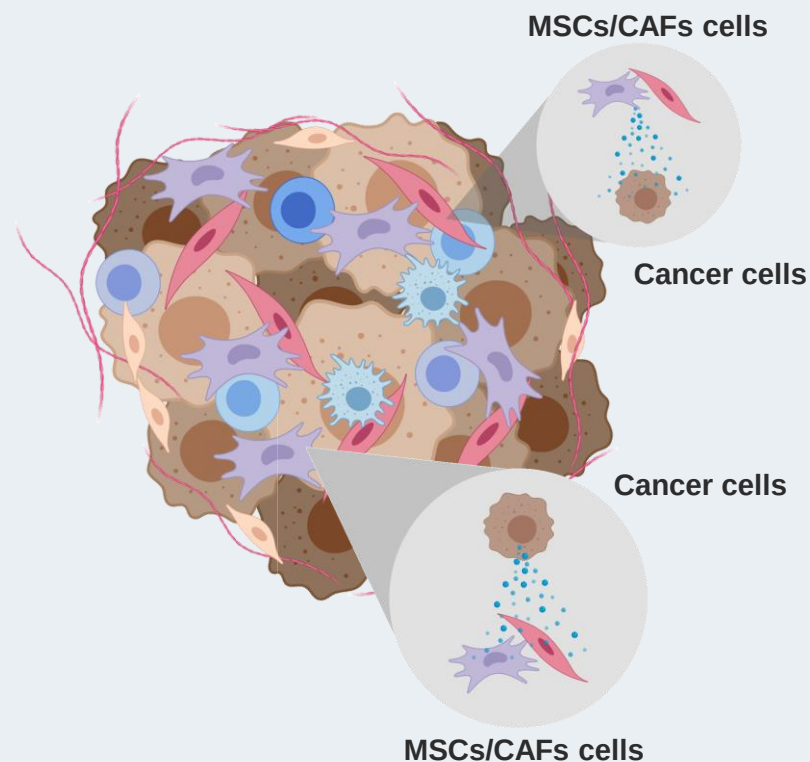
Activation of mesenchymal stem cells by macrophages promotes tumor progression through immune suppressive effects

Xiao-hua Jia¹, Guo-wei Feng^{2,4,5}, Zhong-liang Wang³, Yang Du¹, Chen Shen¹, Hui Hui¹, Dong Peng^{1,2}, Zong-jin Li⁴, De-ling Kong⁵, Jie Tian^{1,6}

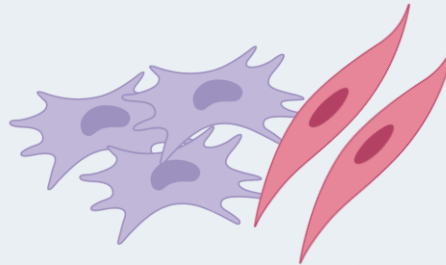
Mesenchymal stem cells within tumour stroma promote breast cancer metastasis

Antoine E. Karnoub¹, Ajeeta B. Dash², Annie P. Vo¹, Andrew Sullivan², Mary W. Brooks¹, George W. Bell¹, Andrea L. Richardson¹, Kornelia Polyak¹, Ross Tubo² & Robert A. Weinberg¹nature
ARTICLES

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- **Ceritinib:** works by targeting ALK receptor found on the cancer cells
 - **Crizotinib:** works by targeting ROS1/c-Met and ALK receptors found on the cancer cells
- (Chiang *et al.*, 2016)



Stroma may play a key role
in CCA initiation, progression
and invasion

MSCs/CAFs appear to be
one of the most prominent
components of the CCA

What is the **influence** of MSCs/CAFs
on proliferation, invasion and drug
sensitivity in CCA?

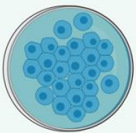


Which are the **paracrine signalling
pathways** driving these changes in
CCA biology?

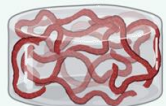
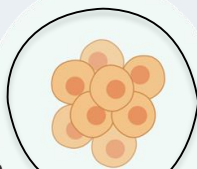
Can we apply this knowledge to investigate the potential
clinical utility of **targeted agents** and drug combinations in
CCA?

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2D Models



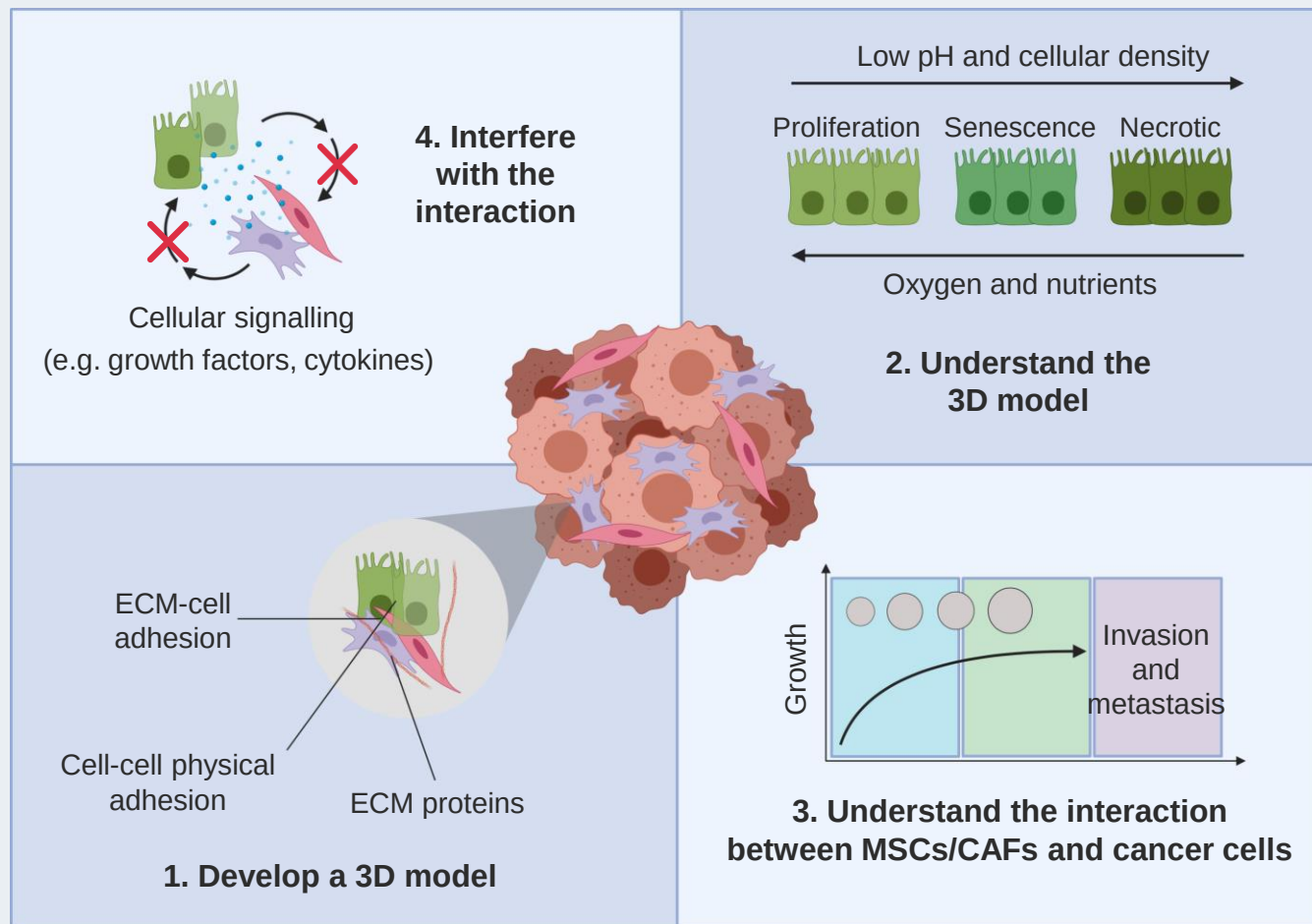
3D Models



In vivo Models



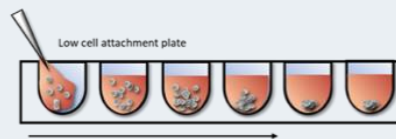
Cellular complexity



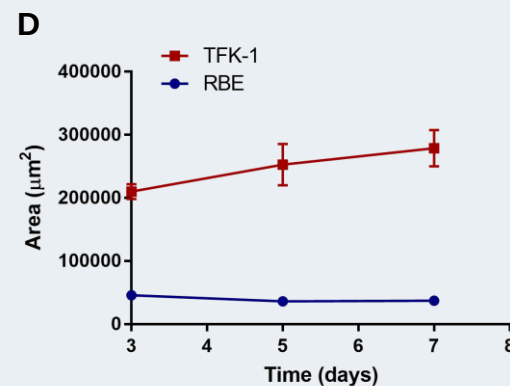
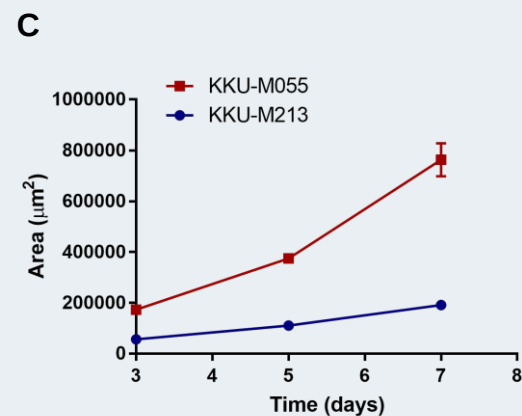
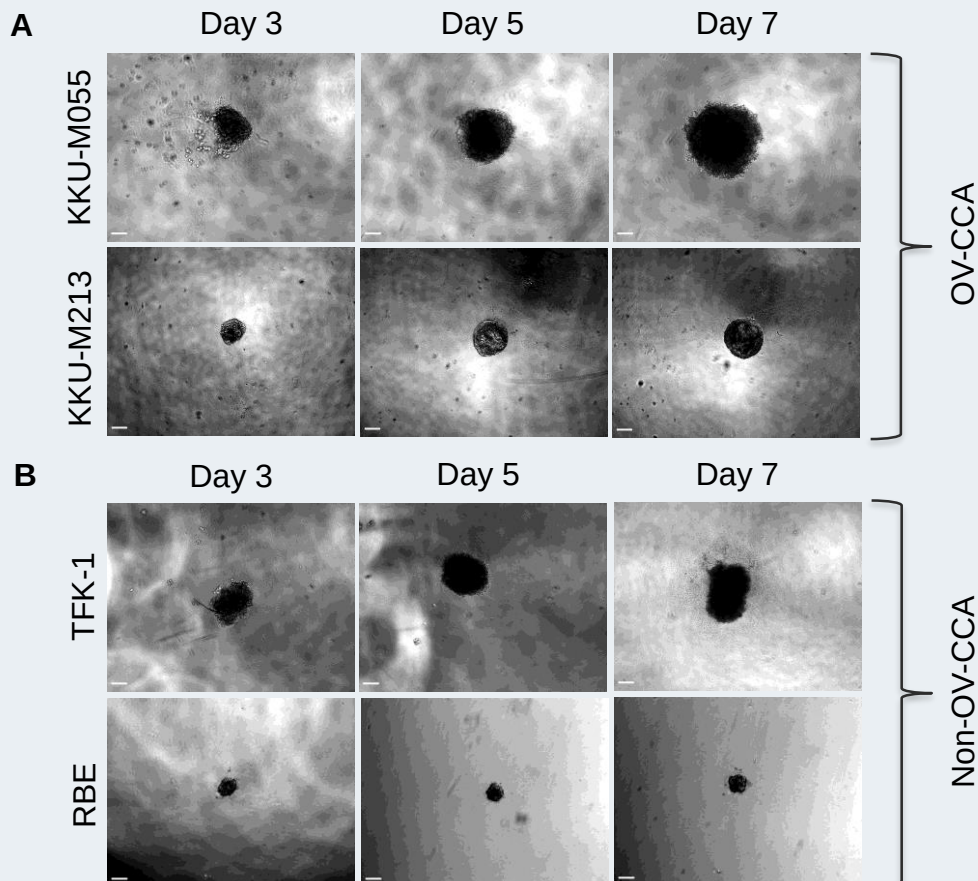
(Costa et al., 2016)

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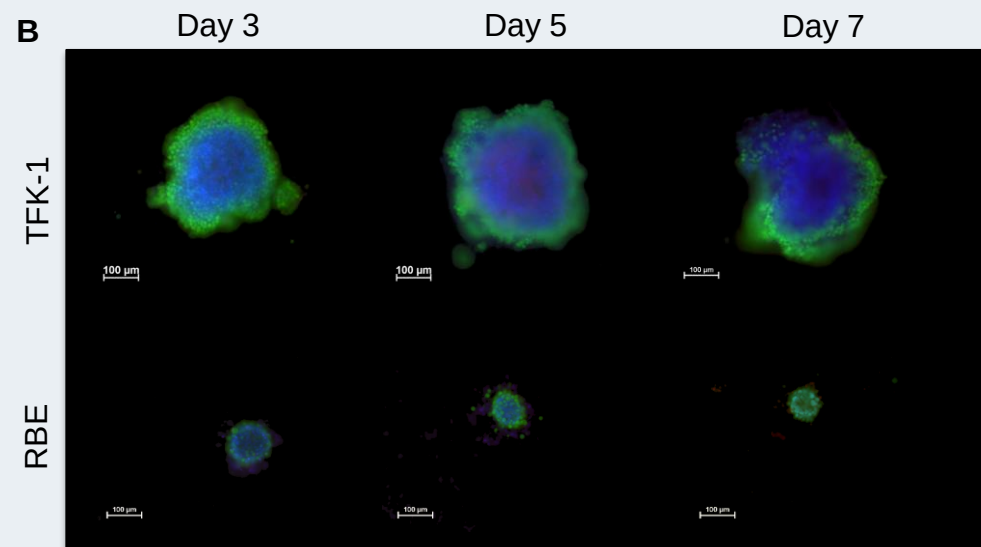
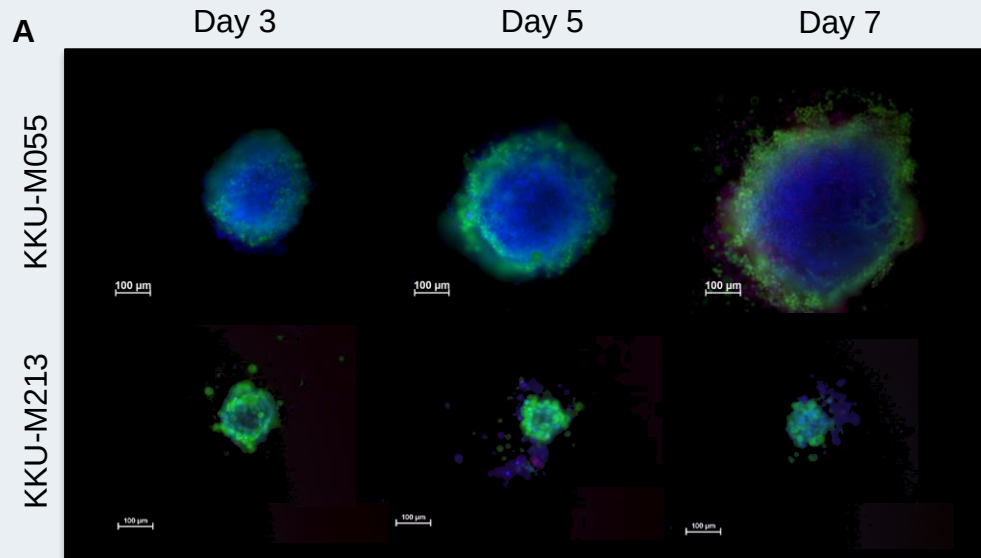
Establishment of CCA cell-lines-derived spheroids



(Kunz-Schughart et al., 2004)



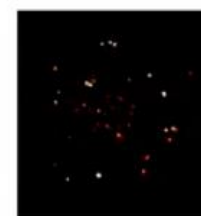
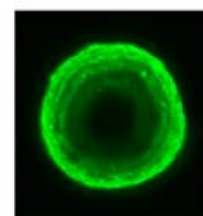
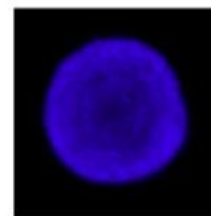
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**Study the viability of the cells in the 3D model**

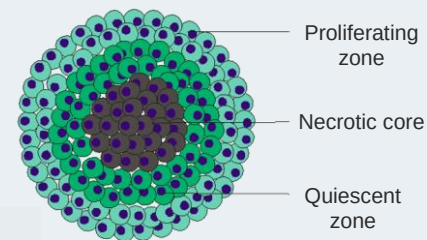
Hoechst - Nuclei

Calcein-AM - Live

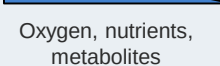
PI - Dead



(Acland et al., 2018)



(Vadivelu et al., 2017)

Metabolic waste, CO₂Oxygen, nutrients,
metabolites

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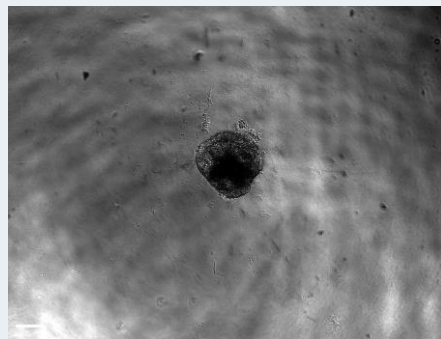
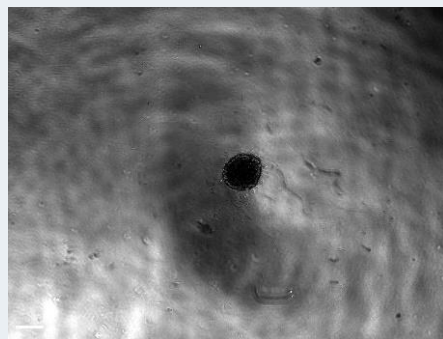
A

Non-OV-CCA

OV-CCA

RBE

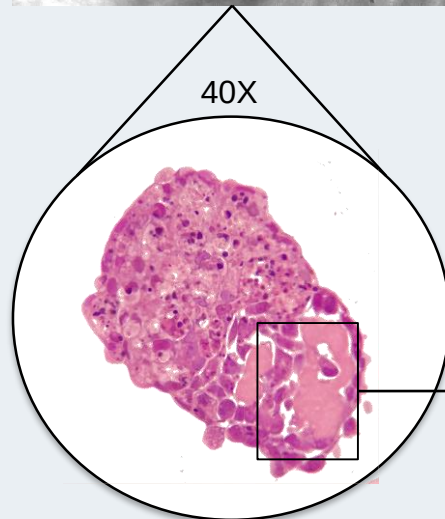
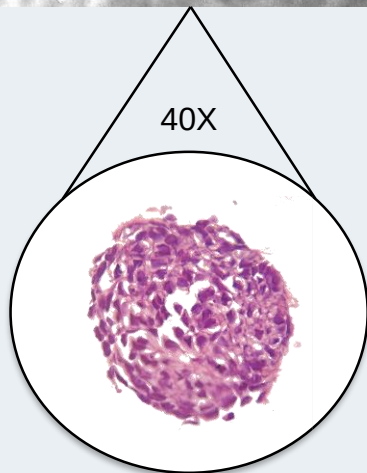
KKU-M213



40X

40X

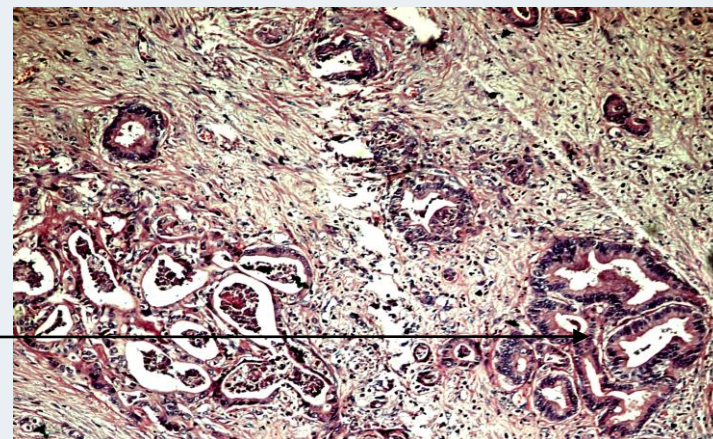
H&E

Immunohistological assessment of the CCA
spheroids

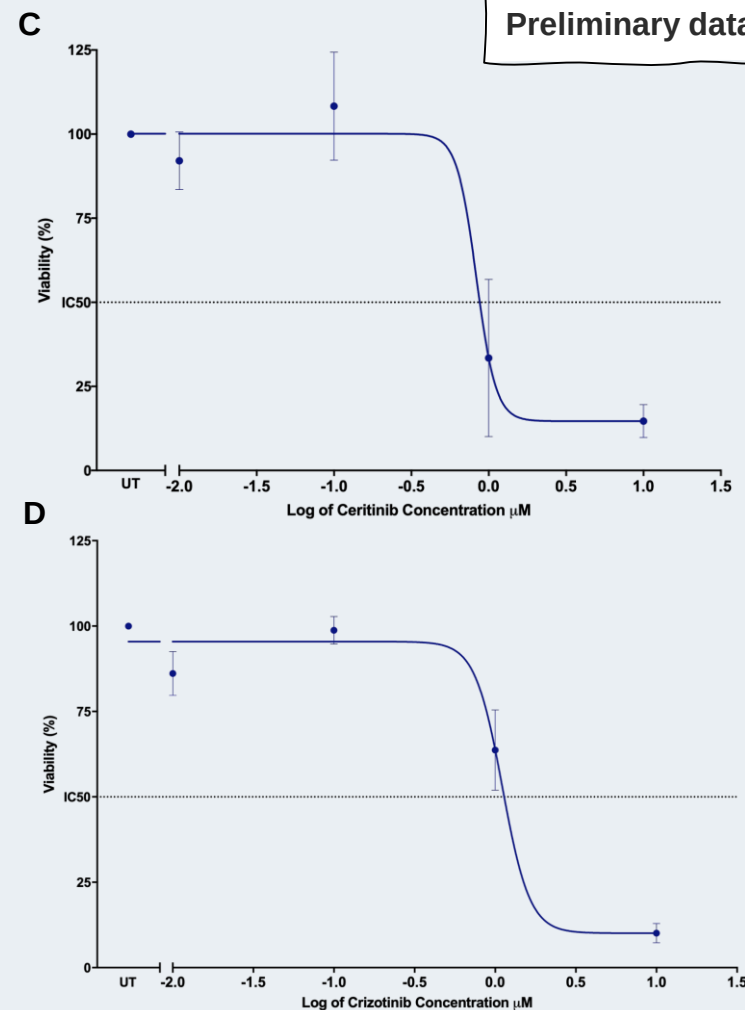
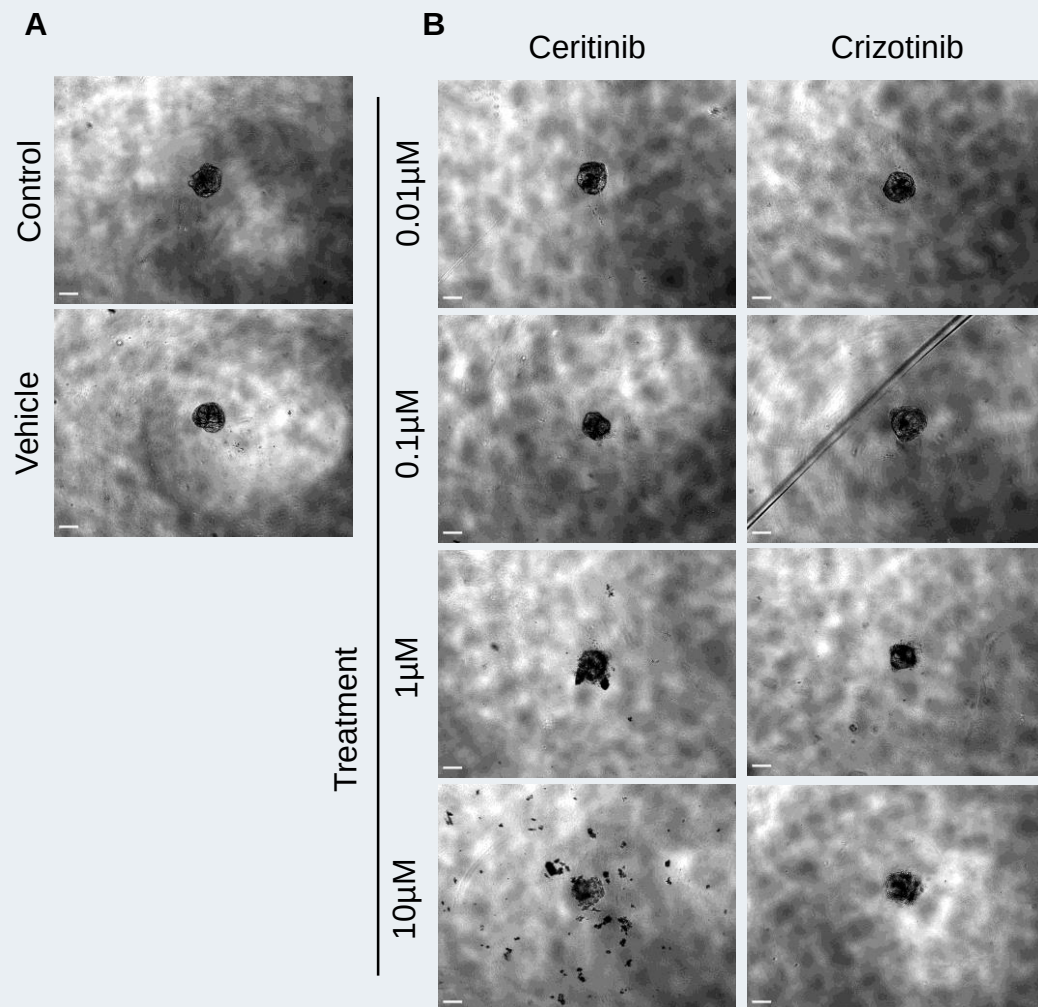
(Ivanov and Grabowska, 2017)

B

Human CCA

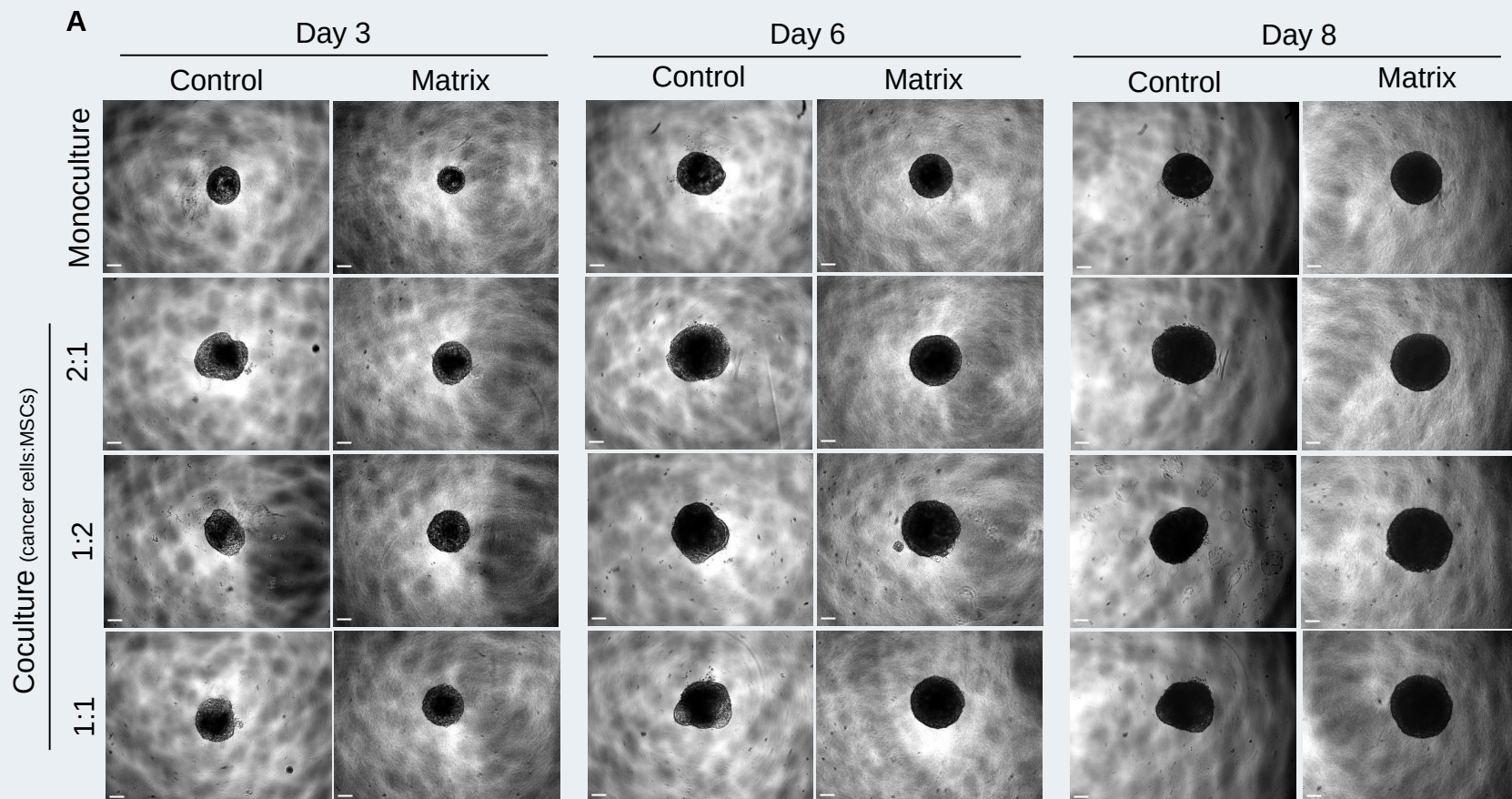


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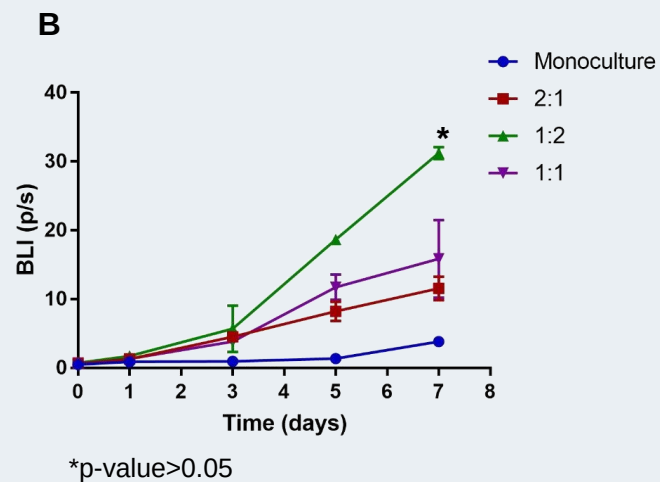
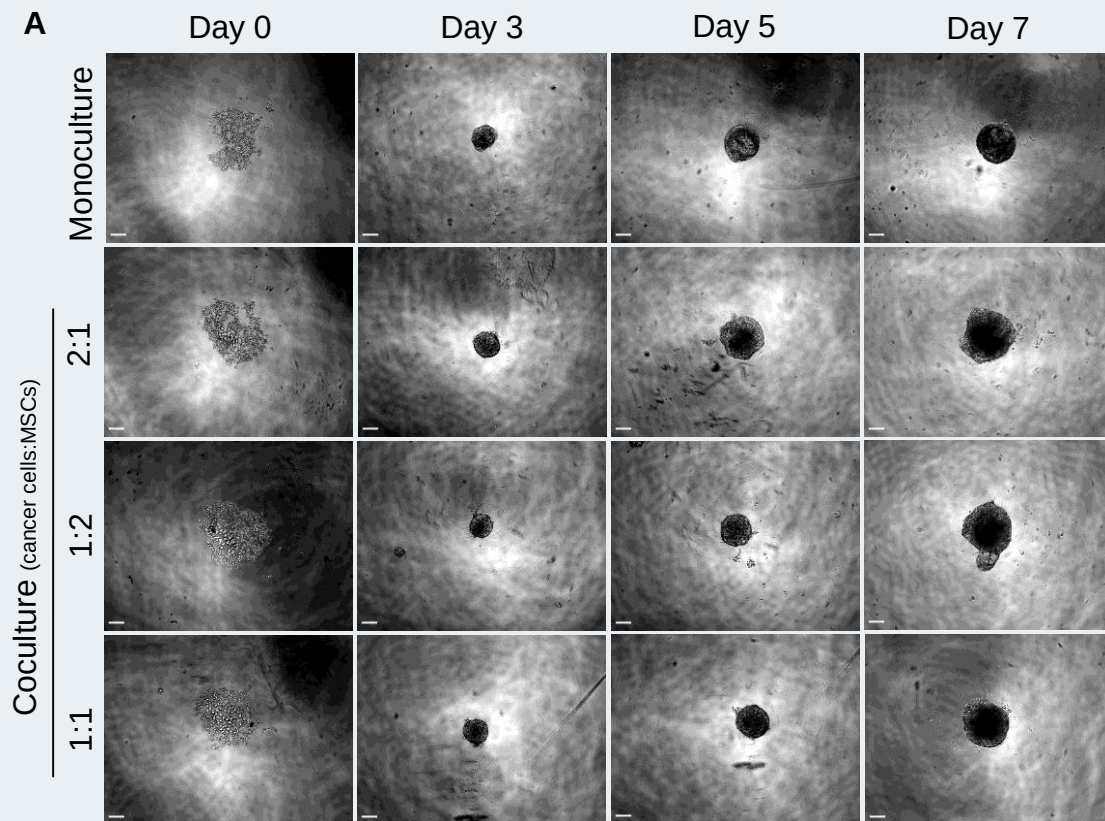
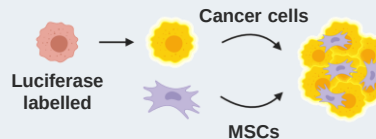
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Determination of the ability of the CCA cells to
invade in presence/absence of MSCs



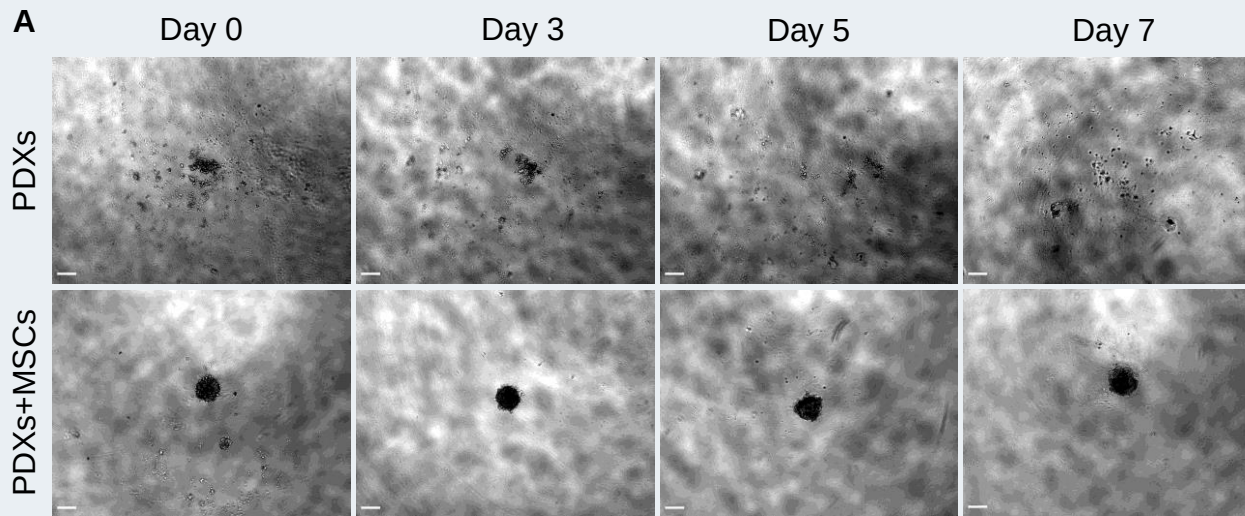
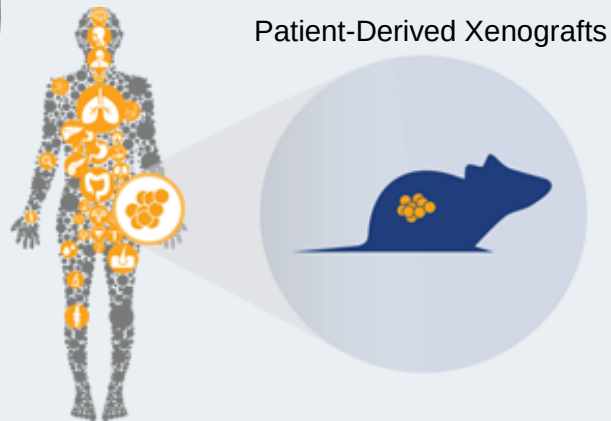
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Determination of the ability of the CCA cells to proliferate in presence/absence of MSCs

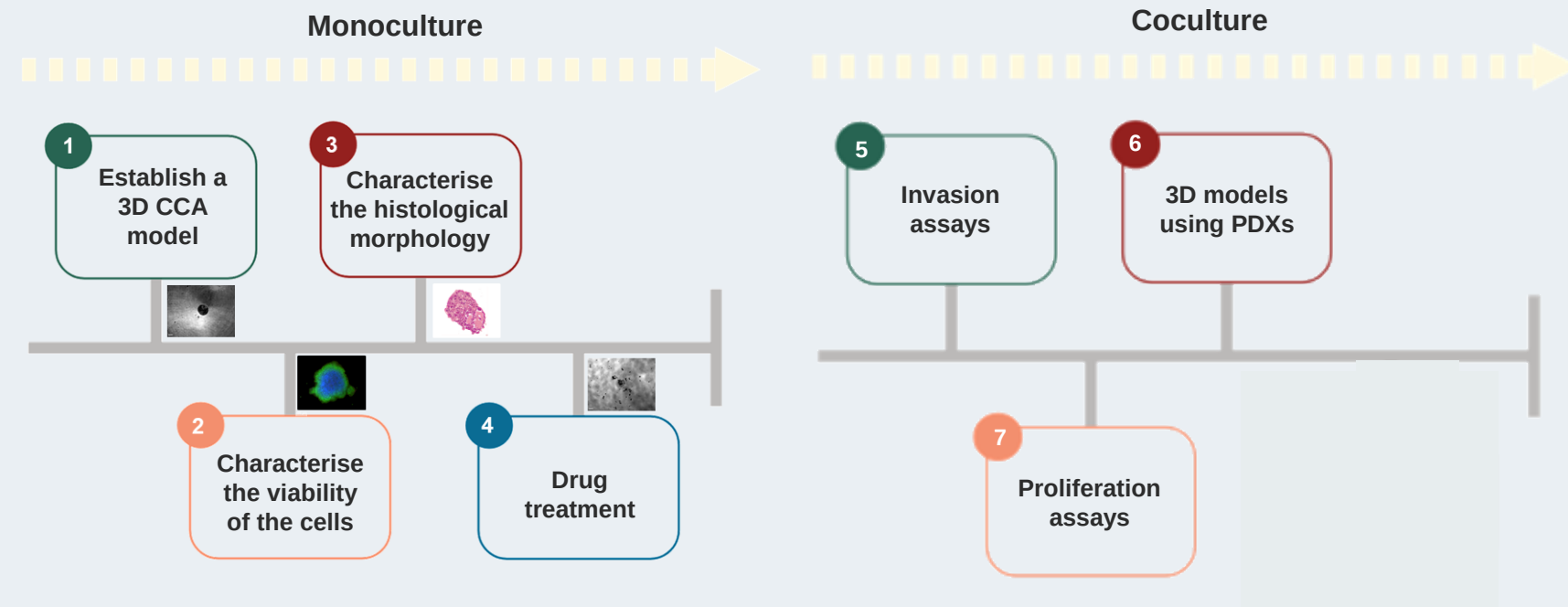


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Preliminary data



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➤ Determine the response to drug treatment when MSCs are present

➤ Identify the signaling pathways driving proliferation

➤ Investigate the effect of MSCs on PDXs-derived spheroids

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Cholangiocarcinoma UK Annual Meeting

Nottingham, November 2019

Thank you!

EVPC Group

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Waraporn Sakaew

Amarnath Pal

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Marian Meakin

Alison Mackie

David O Bates

Isioma Egbuniwe

Kiren Yacqub-Usman

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Faculty of Medicine and Health Sciences EU PhD Scholarship

EVPC Group



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PHARMACOLOGY**

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