

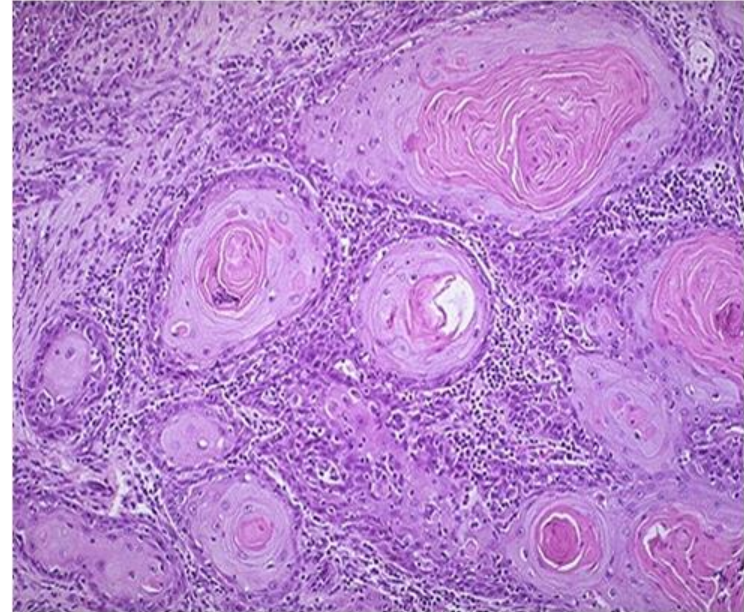
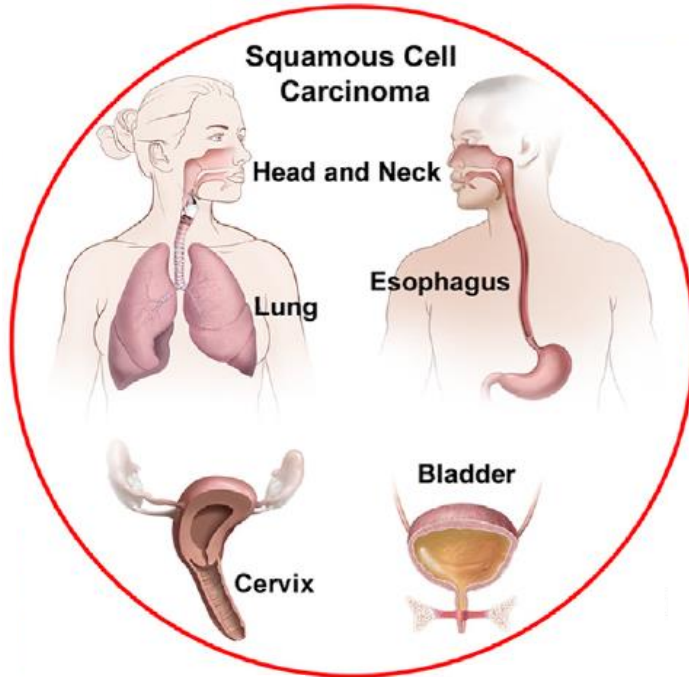
Current knowledge about cancer biology in EB

Andy South, PhD

Disclosures

Consulting	Stock holding	Funding
<i>Onconova Therapeutics</i> <i>Chiesi Farmaceutici S.p.A.</i>	<i>Krystal Biotech Inc.</i> <i>Eliksa Therapeutics</i>	<i>Onconova Therapeutics</i> <i>Chiesi Farmaceutici S.p.A.</i>

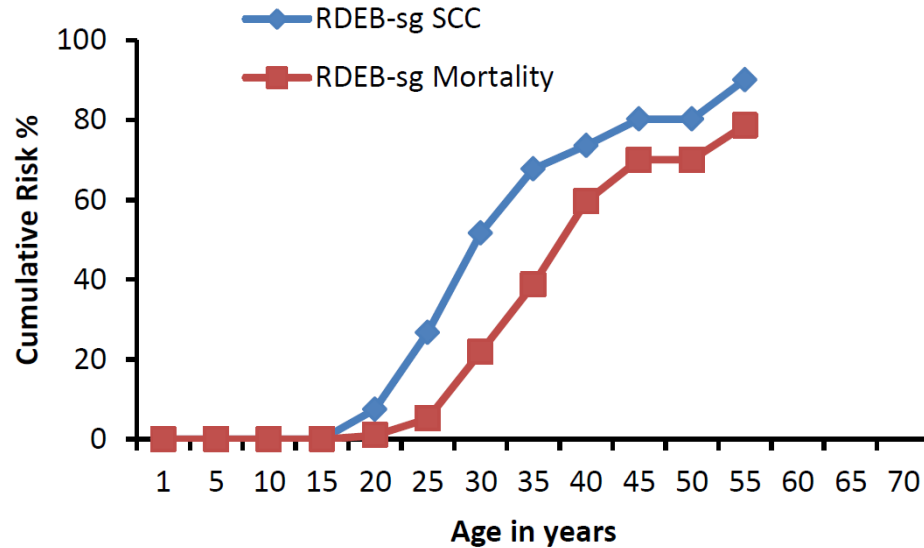
Cancer in EB: Squamous Cell Carcinoma



Campbell et al., 2018, Cell reports 23, 194-212

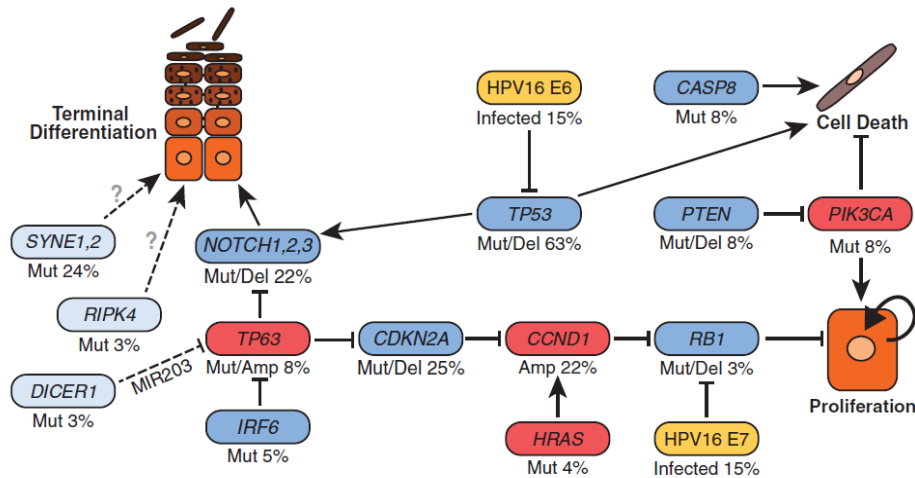
http://oncocancer.blogspot.com/2013_03_01_archive.html

Cancer in EB: Squamous Cell Carcinoma

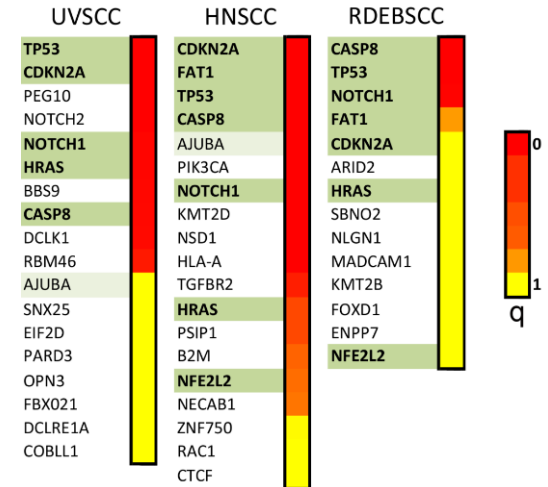


Fine et al, *JAAD* 2009

Cancer in EB: Squamous Cell Carcinoma

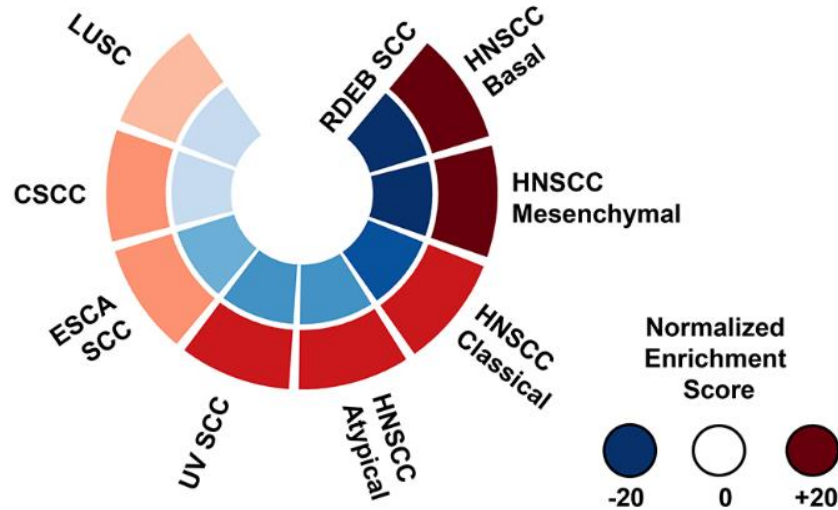


Stransky et al., 2011, Science



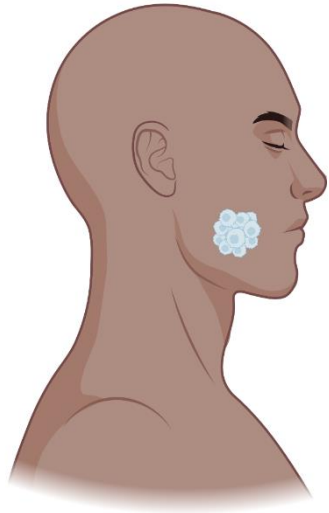
Cho et al, *Sci. Trans. Med.* 2018

Cancer in EB: Squamous Cell Carcinoma

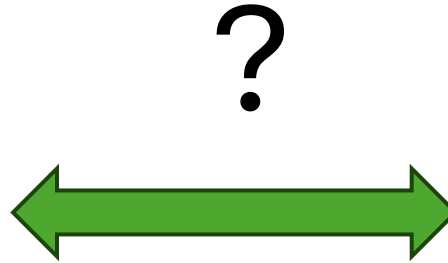


Cho et al, *Sci. Trans. Med.* 2018

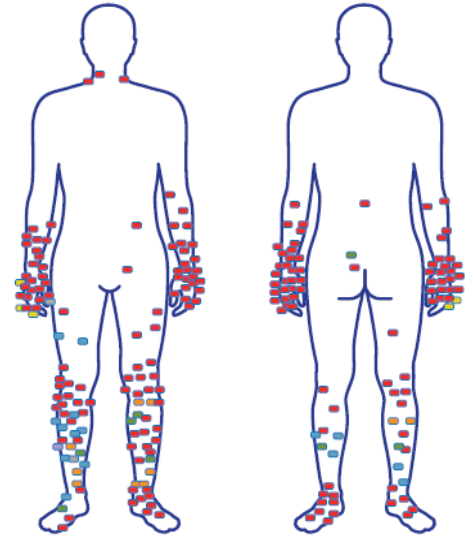
Cross-fertilization of knowledge?



Head and neck SCC



- RDEB-S
- RDEB-Int
- RDEB-Inv
- RDEB-Pru
- DDEB
- JEB-Int
- KEB



Robertson et al, 2021

Is EB cancer a specific entity?

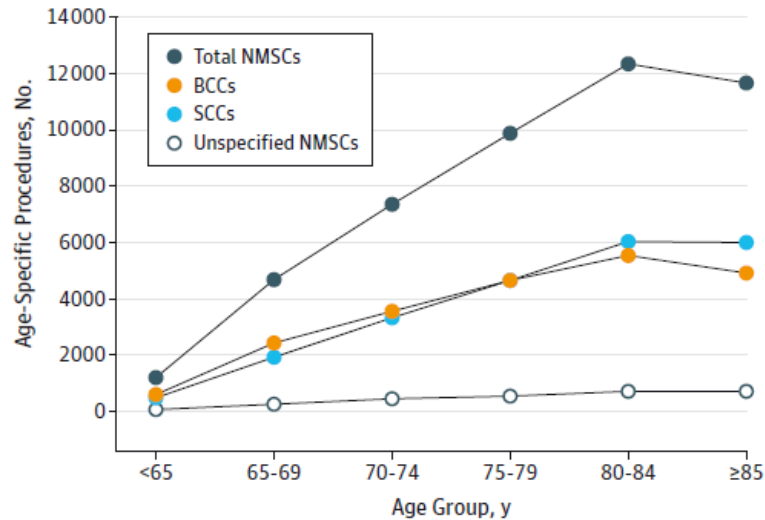
Is EB cancer a specific entity?

Does the FDA and the Office of Orphan Drug Designation consider RDEB SCC as a specific entity?

Could RDEB SCC be considered as a rare sub-type of cutaneous SCC?

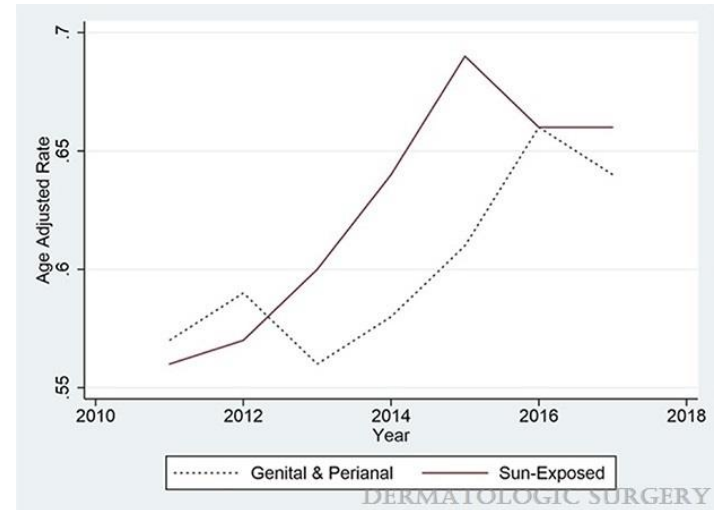
Is EB Cancer a rare sub-type of cutaneous SCC?

Figure. Numbers of Age-Specific Procedures for NMSC per 100 000 Medicare Fee-for-Service Beneficiaries in 2012



Rogers et al., 2015. JAMA Dermatol. 151:1081-1086

Mortality, age adjusted per 100,000 individuals

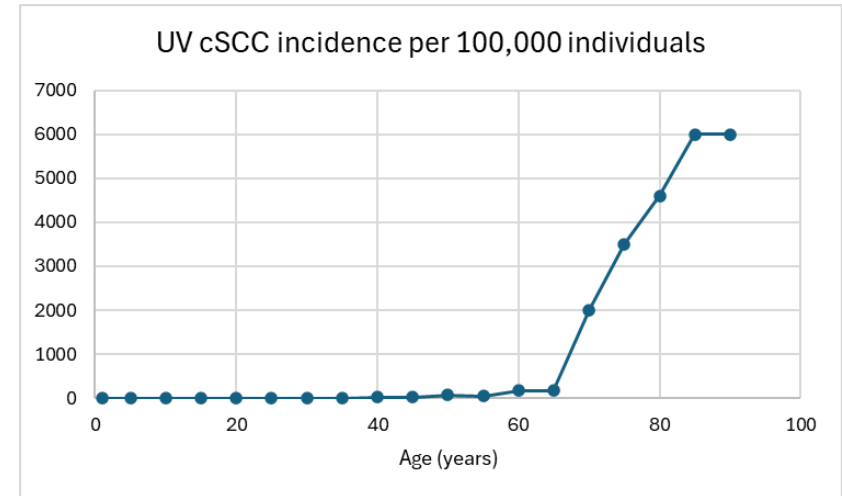
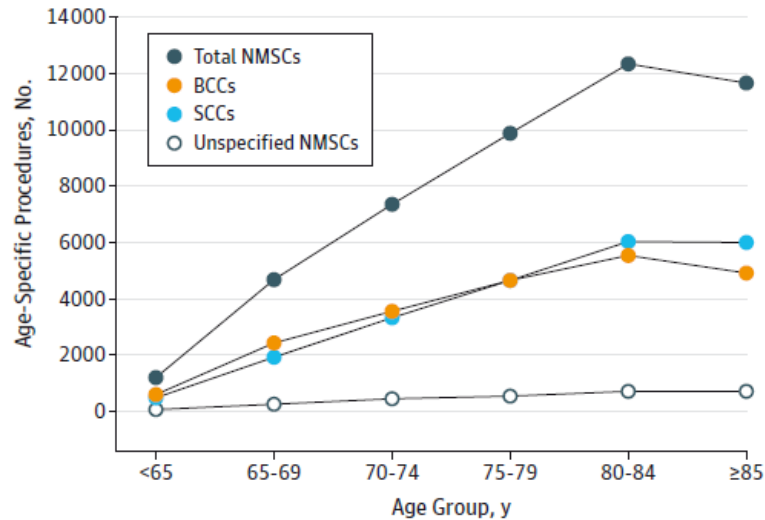


Misztis et al., 2020. Dermatologic Surgery 46:1135-1140

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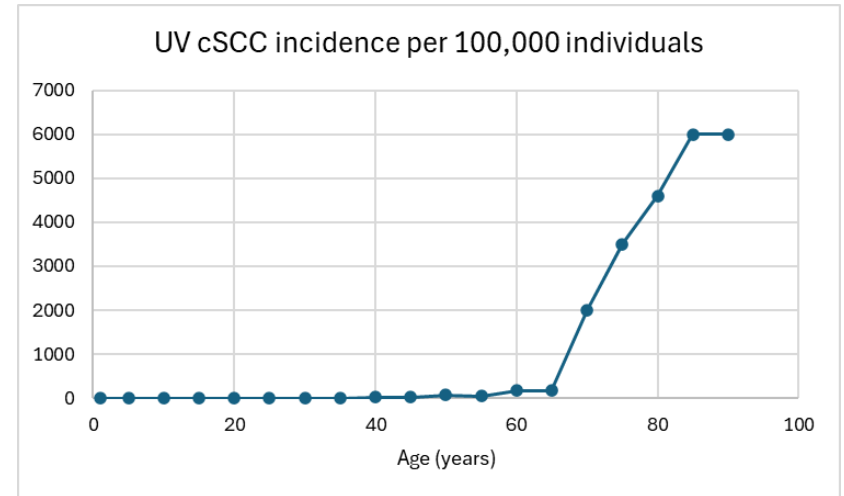
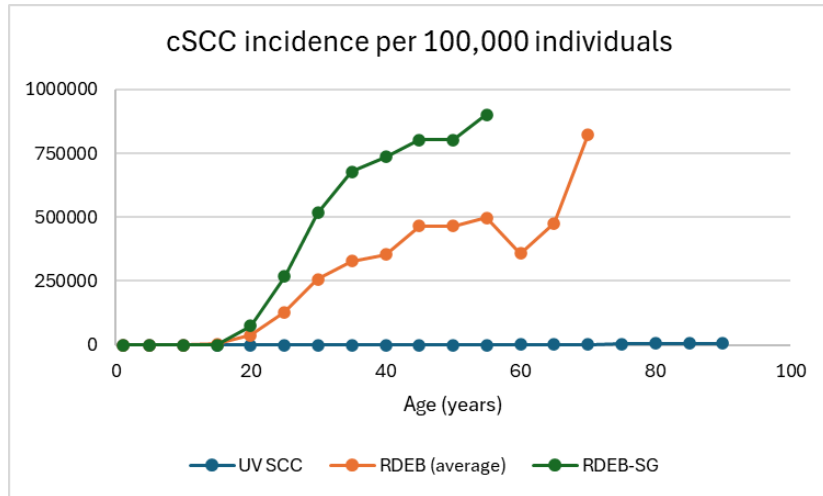
Is EB Cancer a rare sub-type of cutaneous SCC?

Figure. Numbers of Age-Specific Procedures for NMSC per 100 000 Medicare Fee-for-Service Beneficiaries in 2012

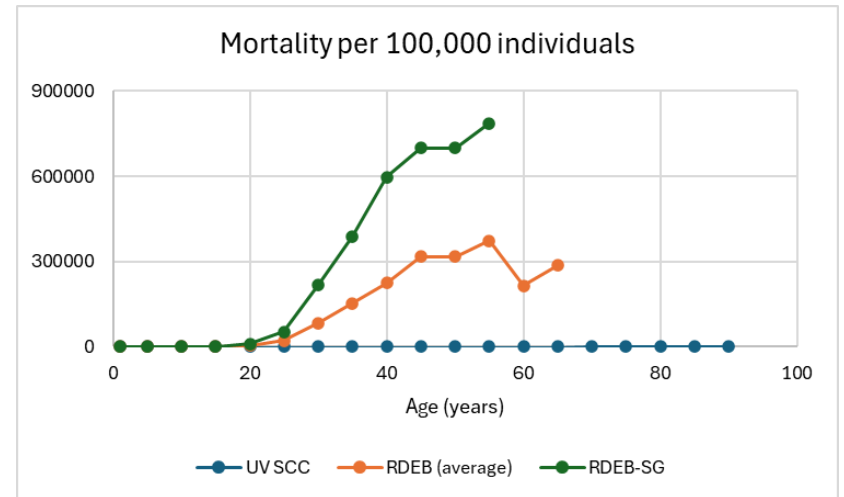
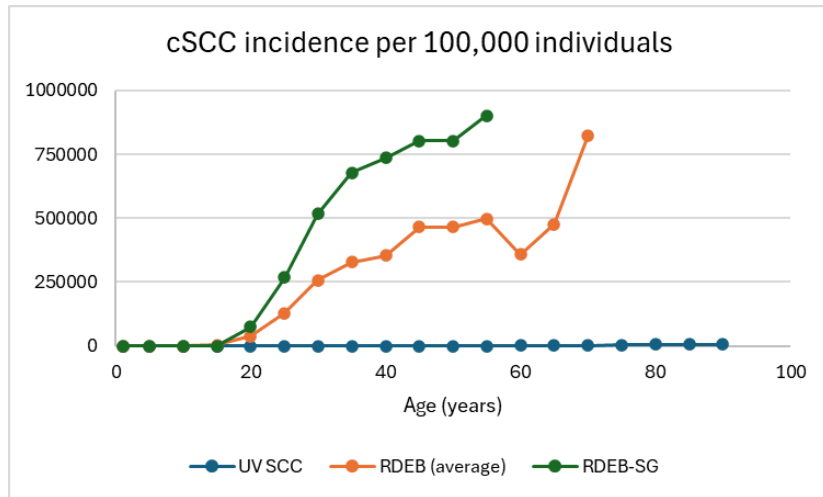


Rogers et al., 2015. JAMA Dermatol. 151:1081-1086

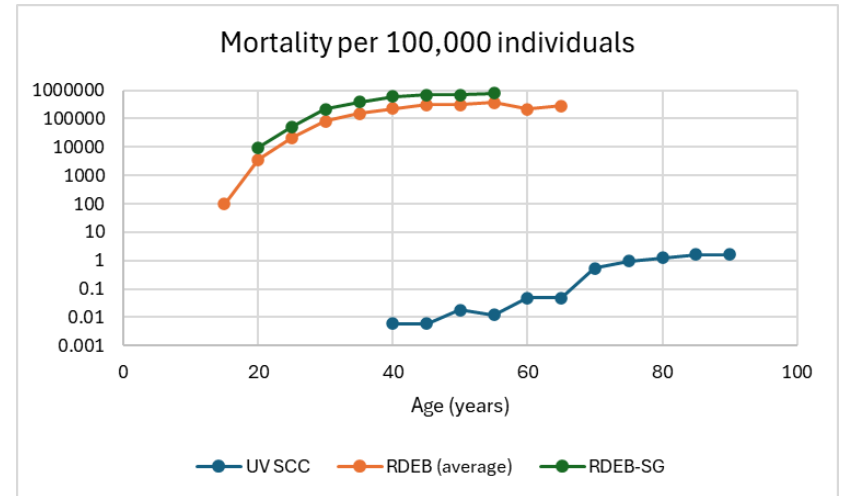
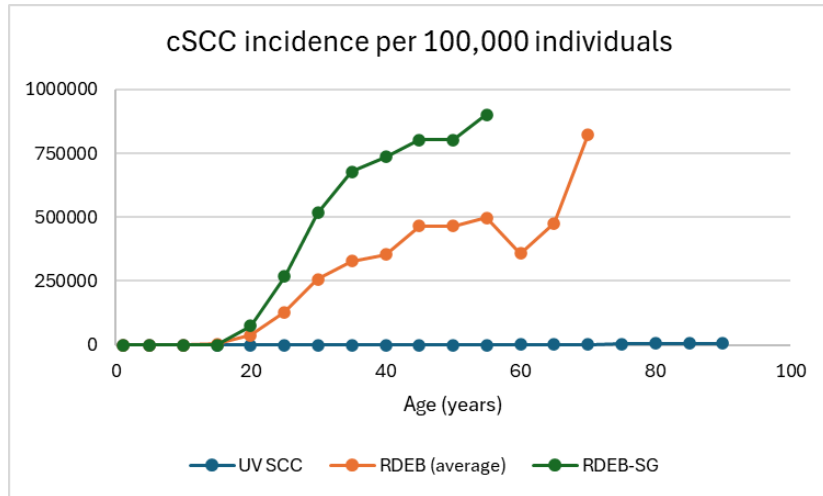
Is EB Cancer a rare sub-type of cutaneous SCC?



Is EB Cancer a rare sub-type of cutaneous SCC?



Is EB Cancer a rare sub-type of cutaneous SCC?

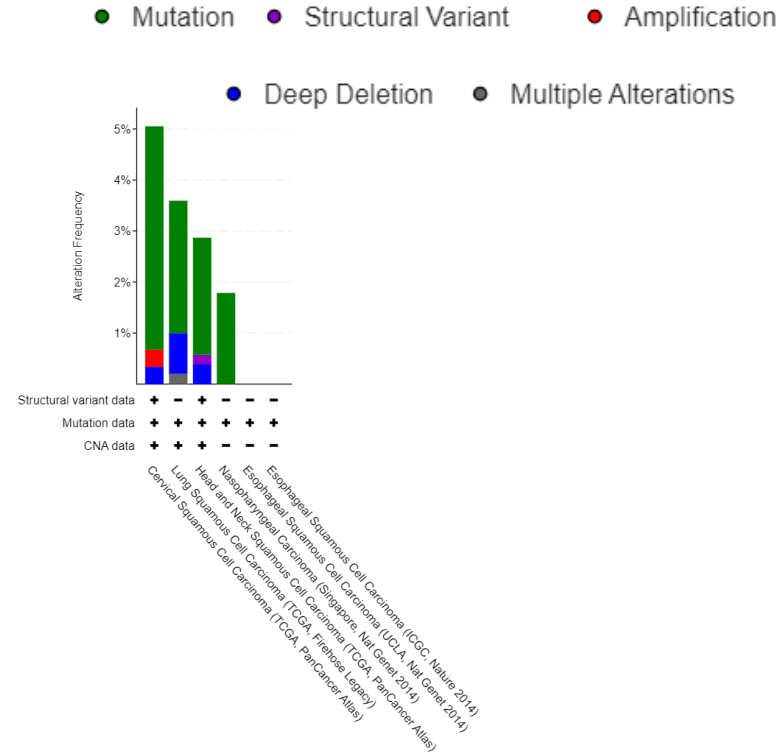


Is EB cancer a specific entity?

Tumors arise on a background of *COL7A1* mutation

Tumors are mutant for *COL7A1*

No other tumor type has *COL7A1* “driver” mutations



Current knowledge about cancer biology in EB

RDEB SCC cancer cells share features with other non-EB SCC cancer cells

RDEB SCC cancers are more similar to other RDEB SCC cancers than to other types of non-EB SCC cancer

Skin in RDEB patients is a “permissive” environment, i.e. the cells surrounding the SCC cancer cells are very different and do not suppress cancer growth to the extent that the same cells in other types of non-EB cancer do

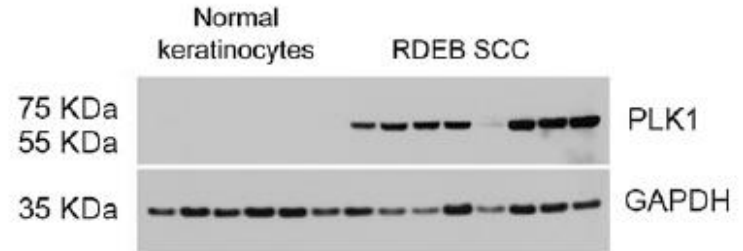
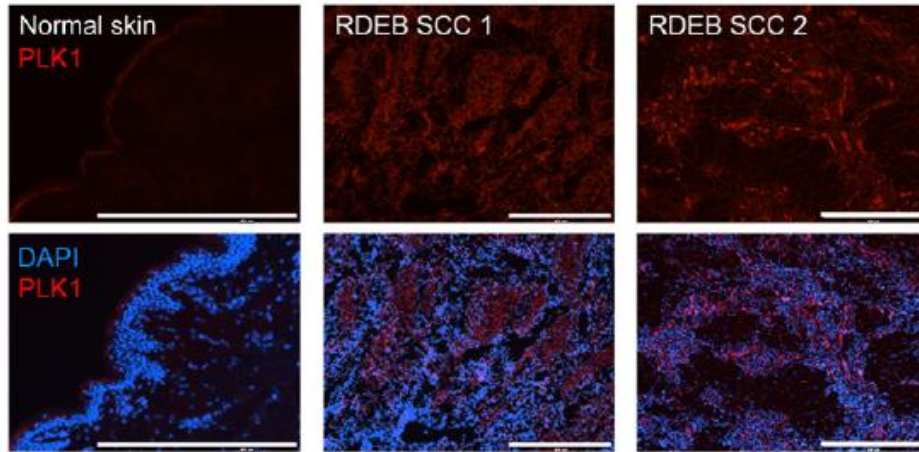
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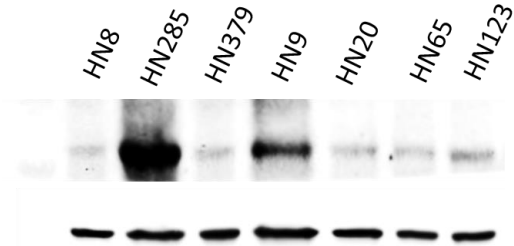
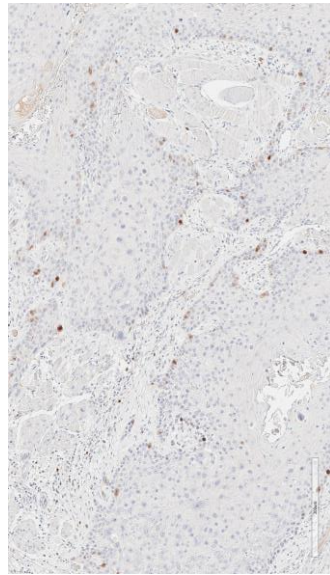
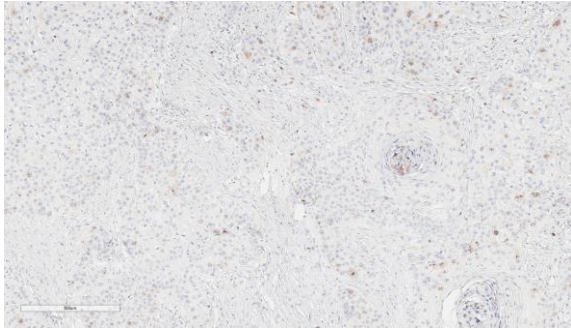
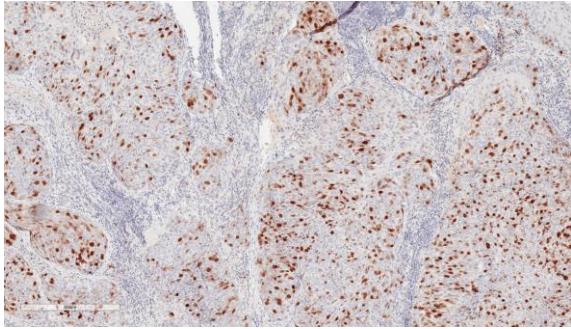
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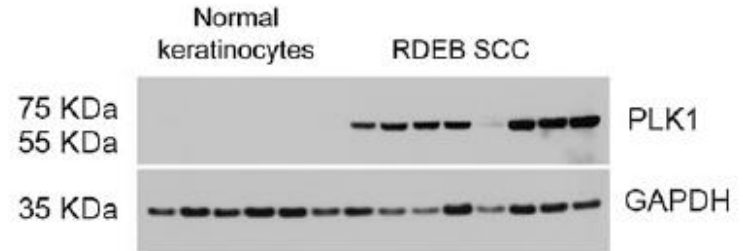
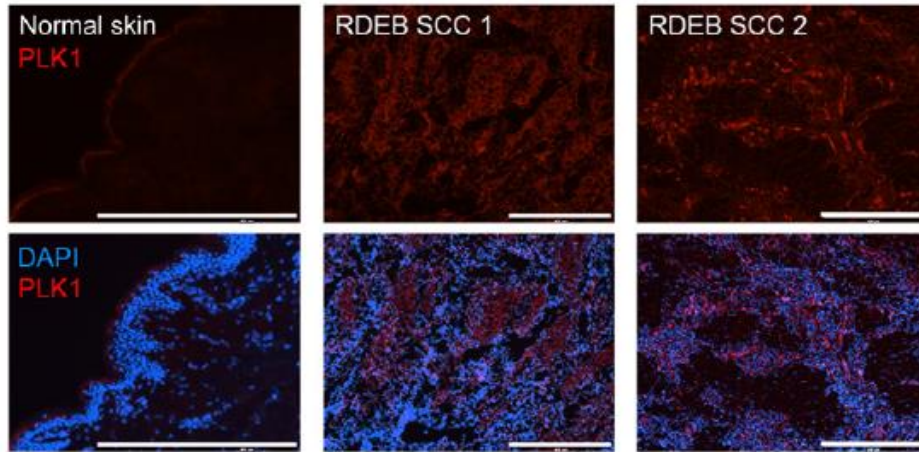
Increased PLK1 expression in RDEB cSCC



Variable/ low PLK1 expression in HNSCC including cSCC



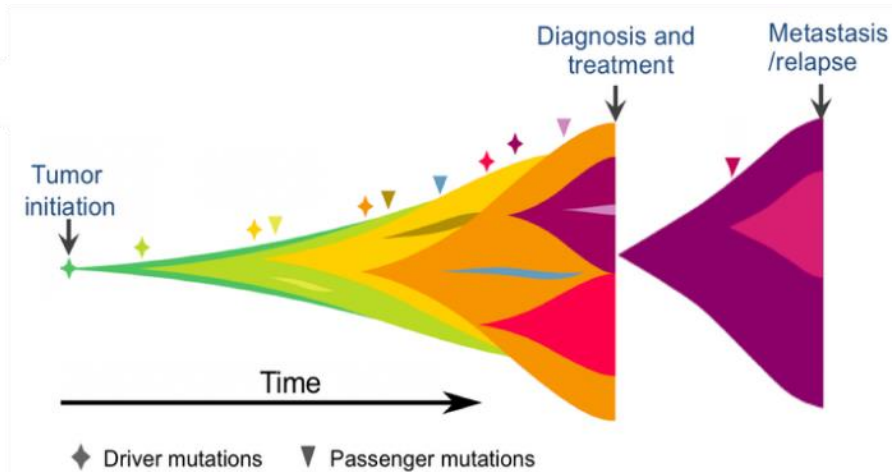
Increased PLK1 expression in RDEB cSCC



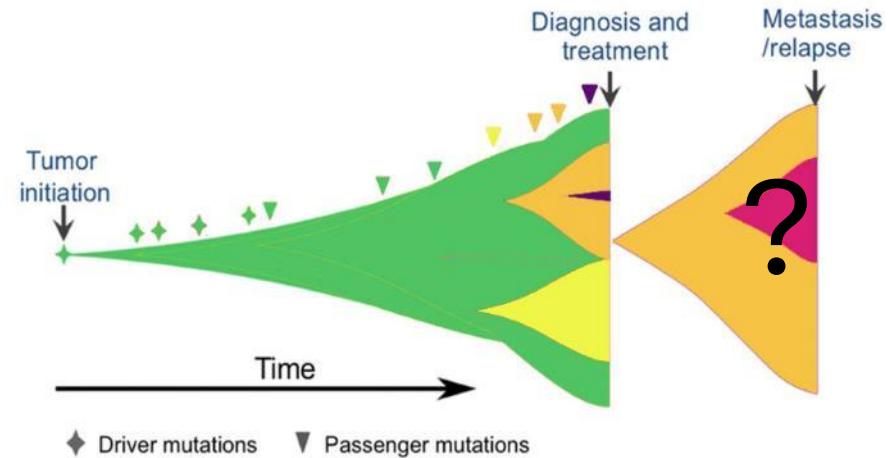
Primary Tumors are Homogenous

Suggesting that they develop in the absence of typical selection pressures

Non-EB SCC

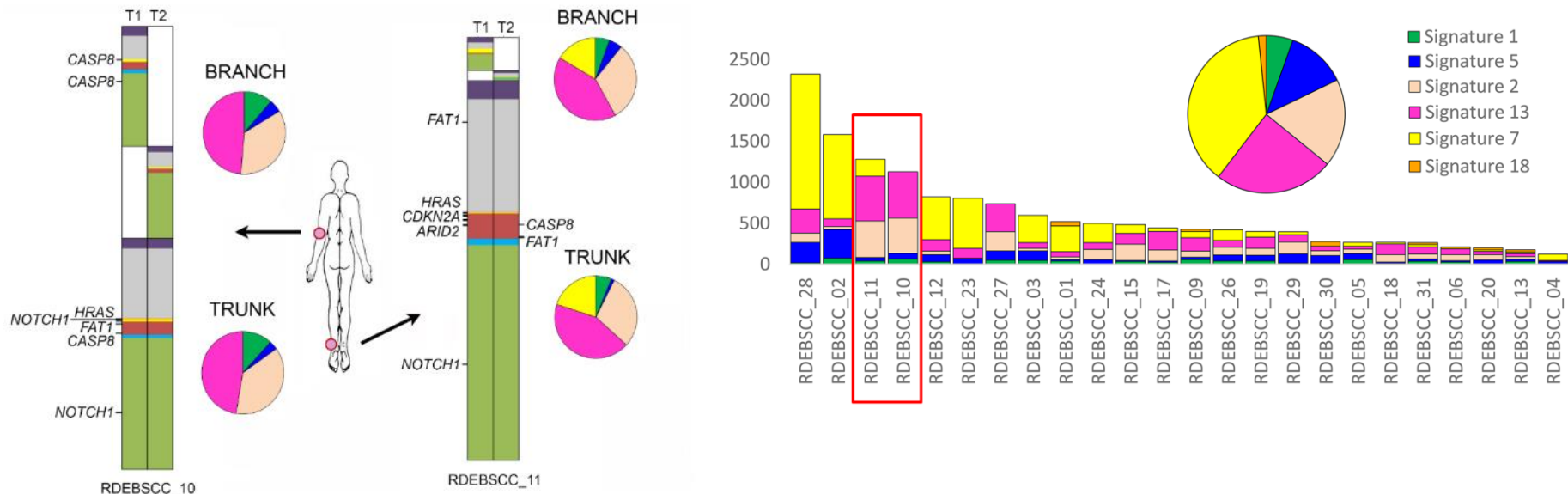


EB SCC



Primary Tumors are Homogenous

Suggesting that they develop in the absence of typical selection pressures



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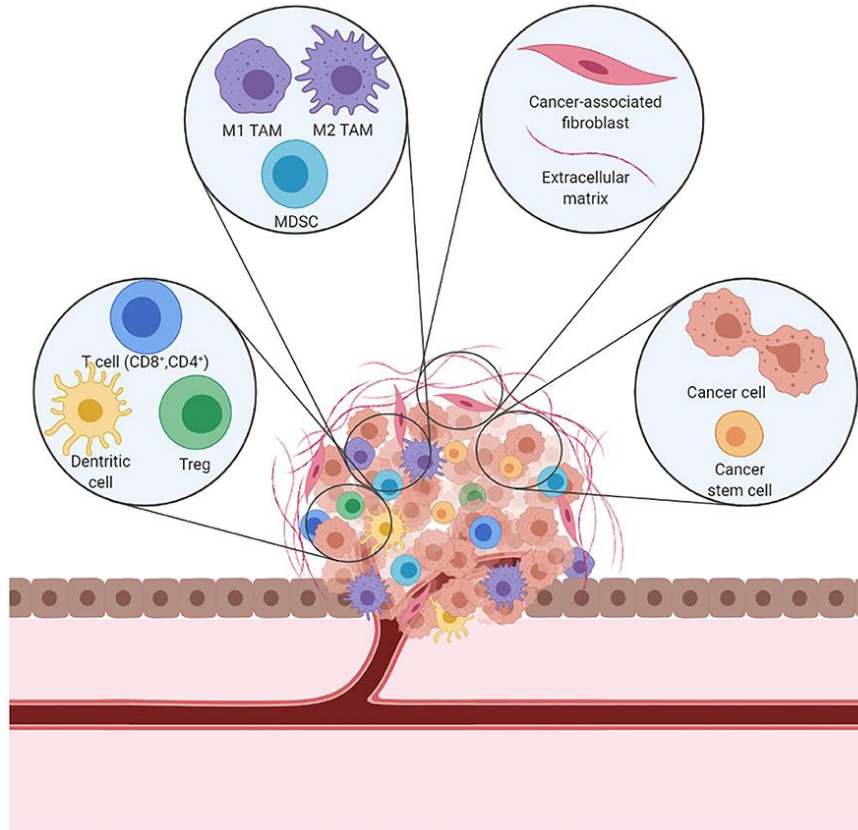
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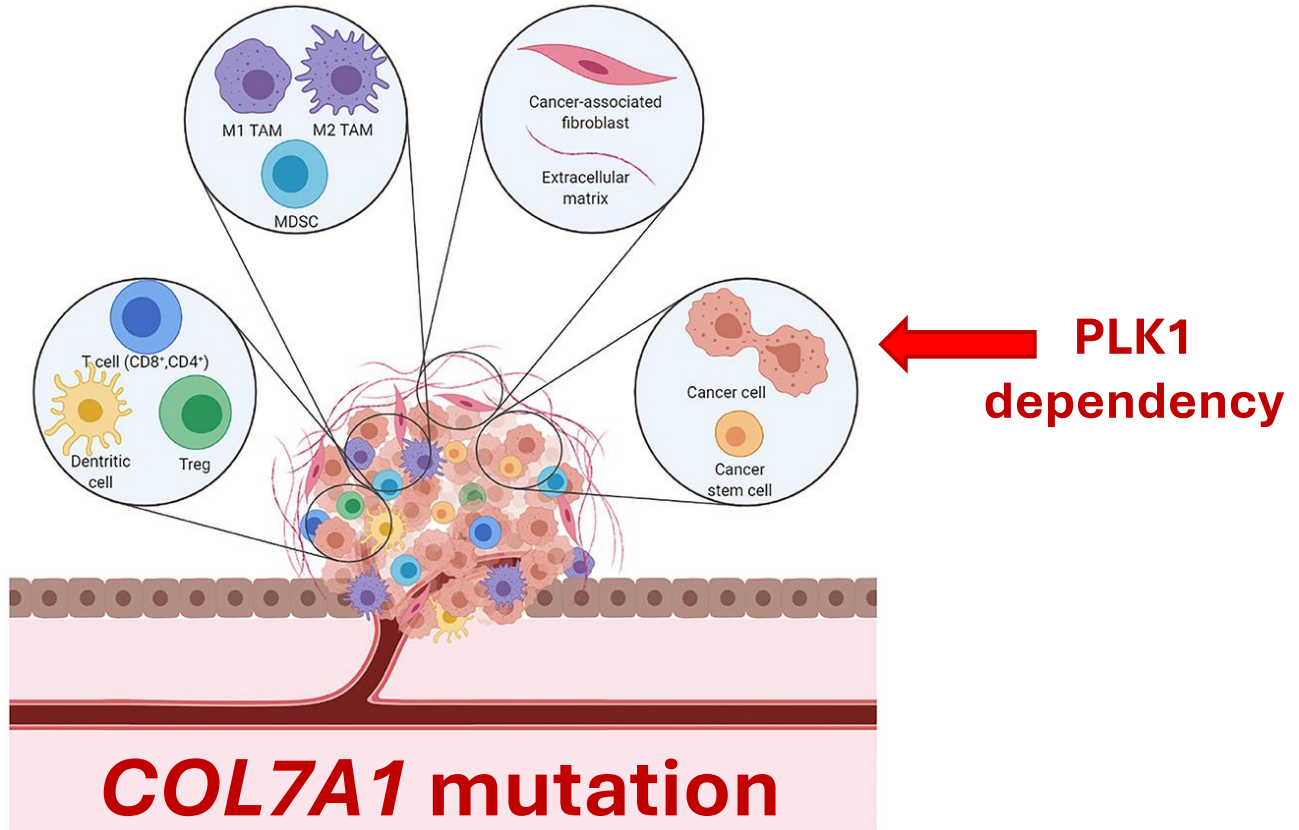
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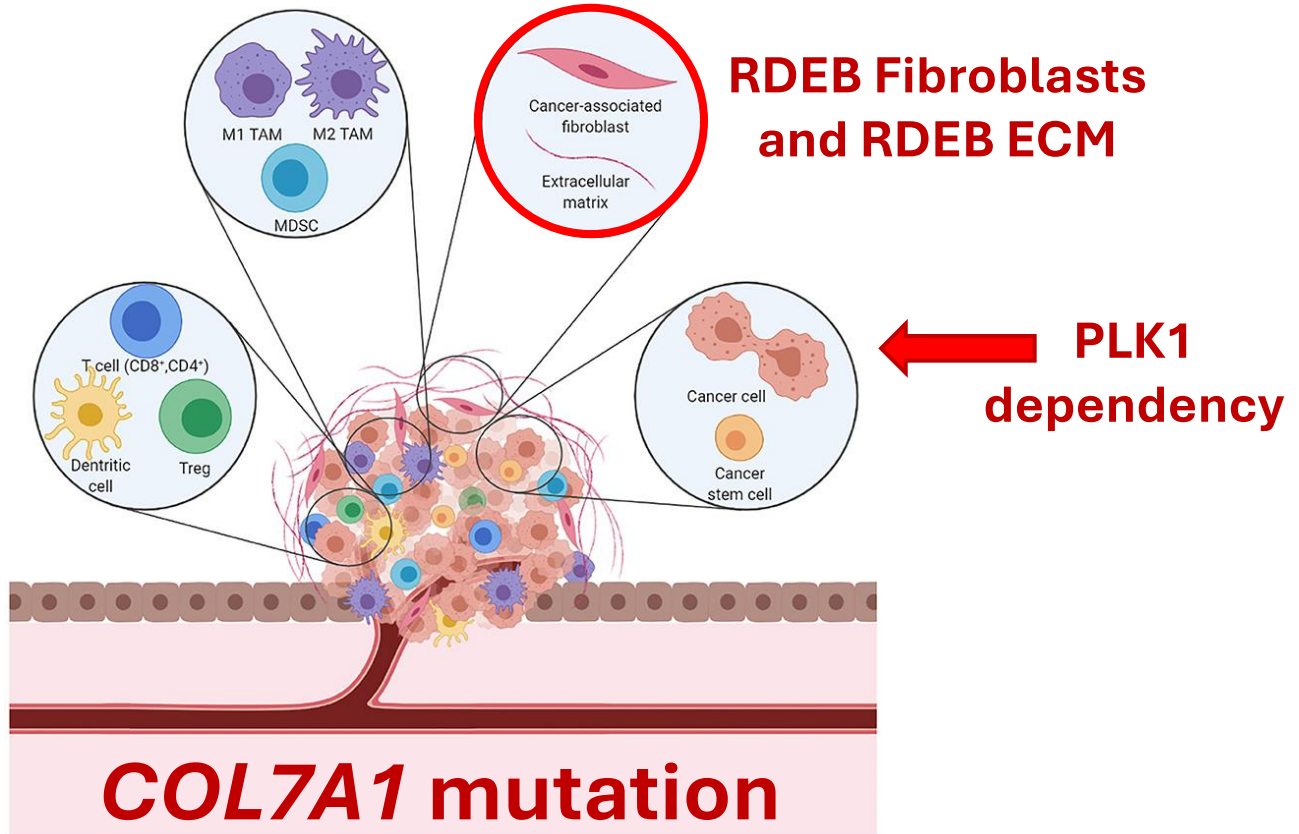
What constitutes a permissive environment?



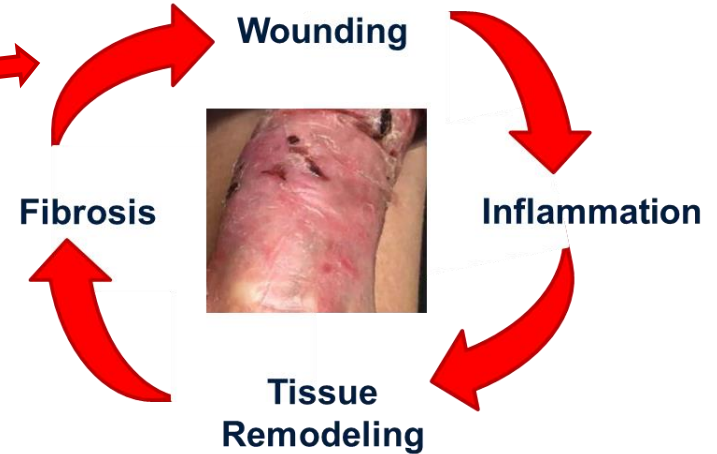
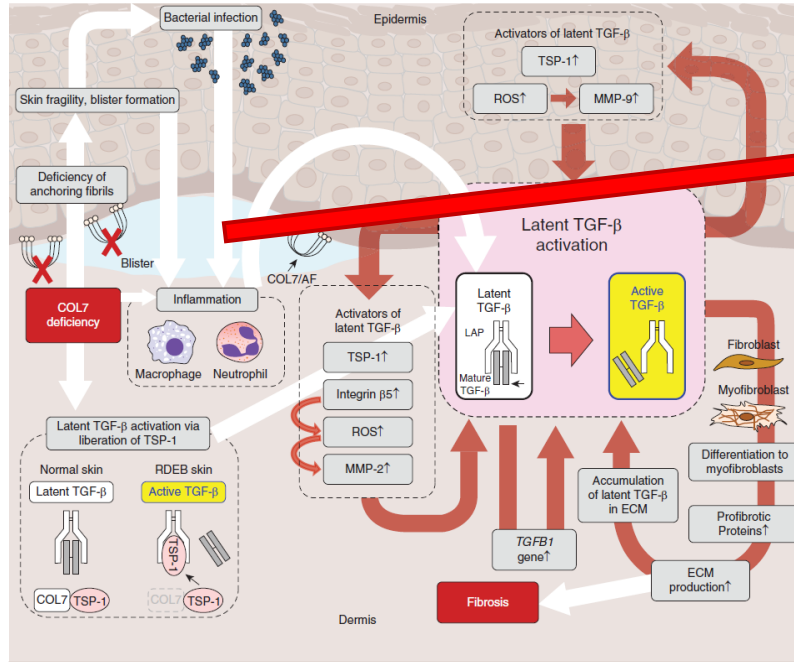
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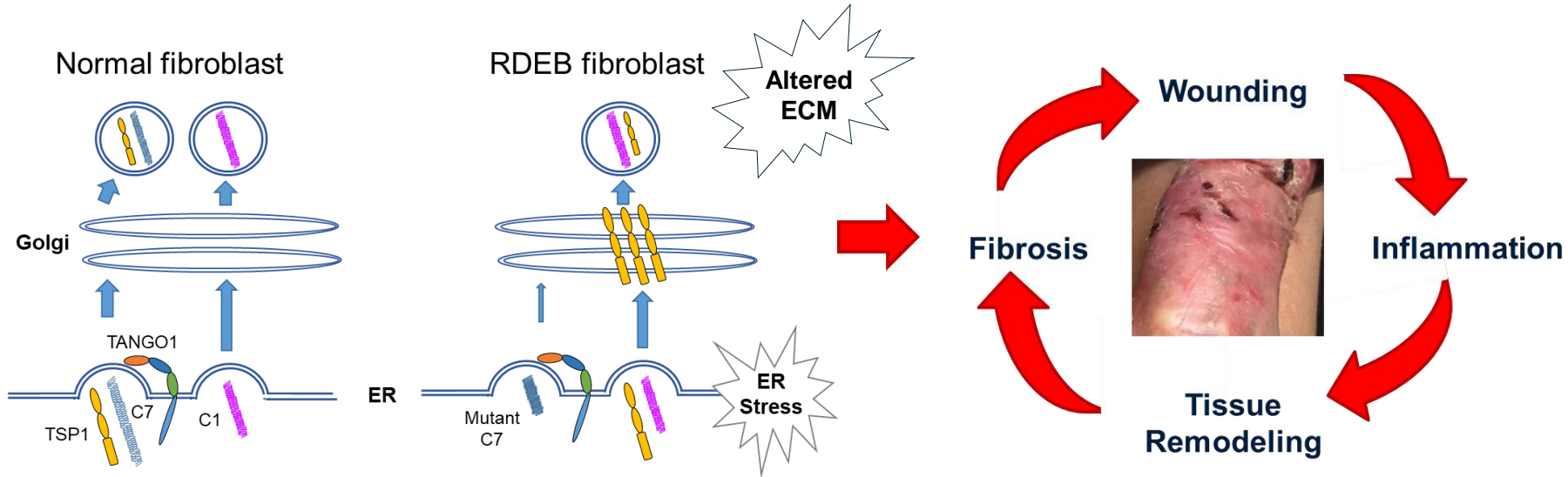


TGF-beta is a driver of EB Cancer



Akasaka et al., 2021 J. Invest. Dermatol. 141:1450-1460

RDEB Fibroblasts are primed for increased TGF-beta signaling and elevated stress



Fibroblasts retain positional information

Diversity, topographic differentiation, and positional memory in human fibroblasts

Howard Y. Chang^{1*}, Jen-Tsan Chi¹, Sandrine Dudoit², Chanda Bondre³, Matt van de Rijn⁵, David Botstein⁶, and Patrick O. Brown^{1,6**}

Departments of ¹Dermatology, ²Biochemistry, ³Pathology, and ⁶Genetics, and ⁴Howard Hughes Medical Institute, Stanford University School of Medicine, Stanford, CA 94305; and ⁵Division of Biostatistics, School of Public Health, University of California, Berkeley, CA 94720

Contributed by Patrick O. Brown, August 14, 2002

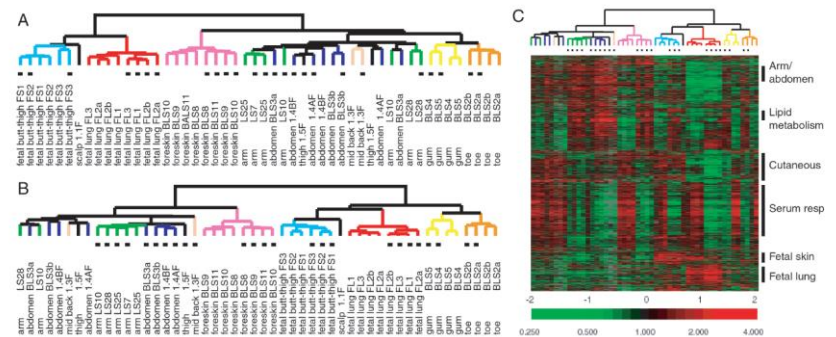
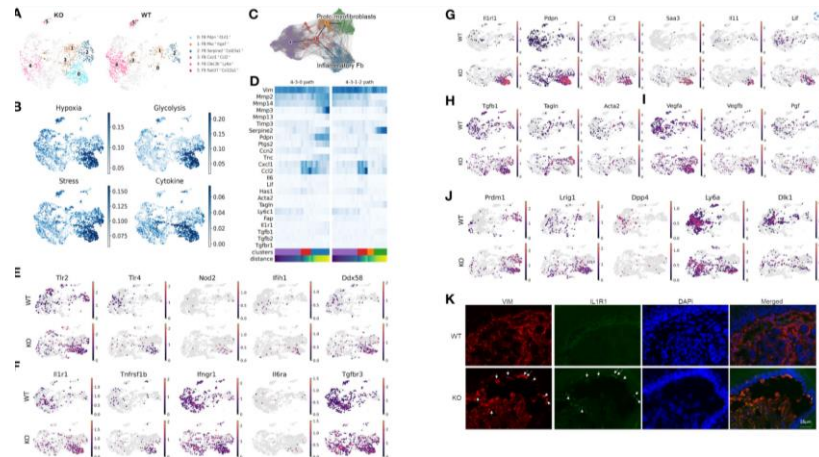


Fig. 1. Topographic differentiation of fibroblasts. (A) Unsupervised hierarchical clustering of cultured fibroblasts. The global gene expression patterns of 50 fibroblast cultures were sorted based on similarity by hierarchical clustering. Approximately 1,400 genes were selected from the total data set based on variance more than 3-fold in at least two arrays. The site of origin of each fibroblast culture is indicated and color-coded. Fibroblasts cultured in minimal-serum medium (0.1% FCS) are indicated by black dots below the dendrogram. (B) Supervised hierarchical clustering of cultured fibroblasts was performed by using approximately 1,600 genes identified by SAM (9) that varied according to fibroblast site of origin. Serum-starved samples are indicated by black dots below the dendrogram. (C) Topography transcriptome of fibroblasts. The variation in expression of approximately 1,600 genes described in B are shown in matrix format (8). The scale extends from 0.25- to 4-fold over mean (-2 to +2 in log₂ space) as is indicated on the bottom. Gray represents missing data. Gene clusters are indicated on the right.

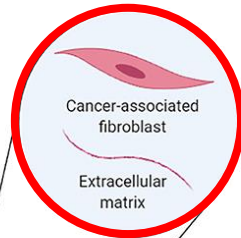
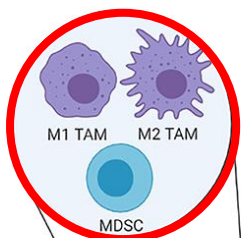
Inflammation-mediated fibroblast activation and immune dysregulation in collagen VII-deficient skin

Morgan Anderson-Crannage^{1,2†}, Alex M. Ascension^{3†}, Olga Ibanez-Sole³, Hongwen Zhu⁴, Edo Schaefer¹, Darcy Ottomaneli⁵, Bruno Hochberg¹, Jian Pan¹, Wen Luo¹, Meijuan Tian¹, Yaya Chu¹, Mitchell S. Cairo^{1,2,5,6*}, Ander Izeta^{3,7*} and Yanling Liao^{3*}

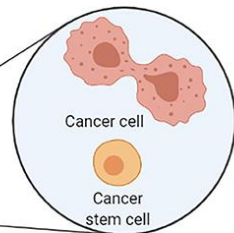
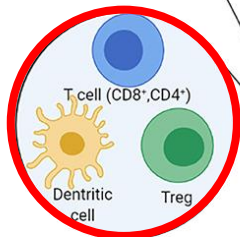


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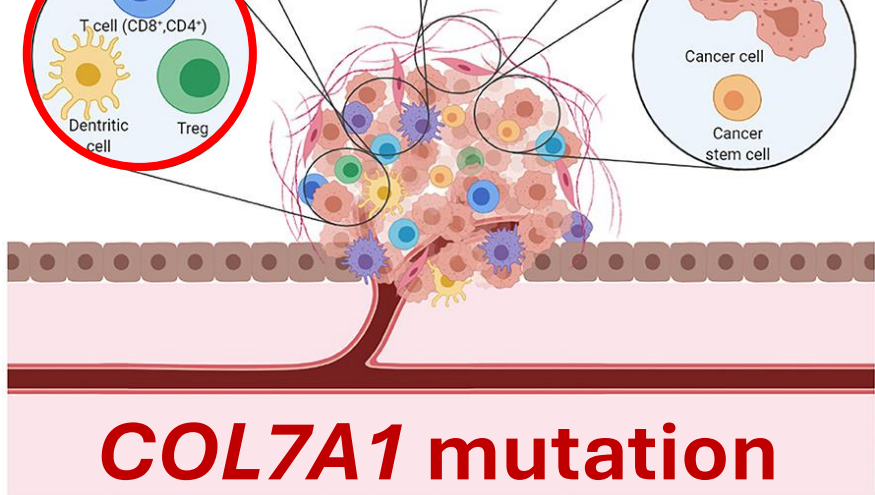
Immune surveillance?



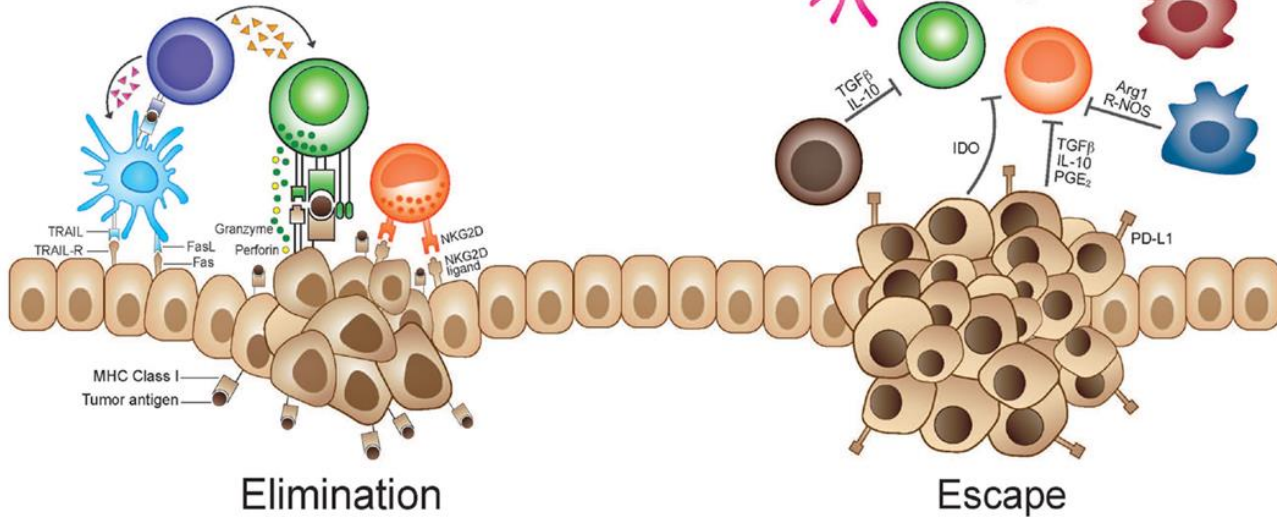
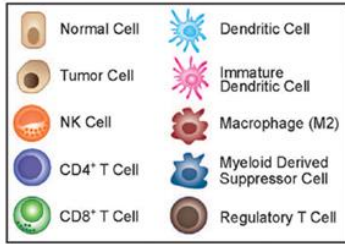
RDEB Fibroblasts and ECM



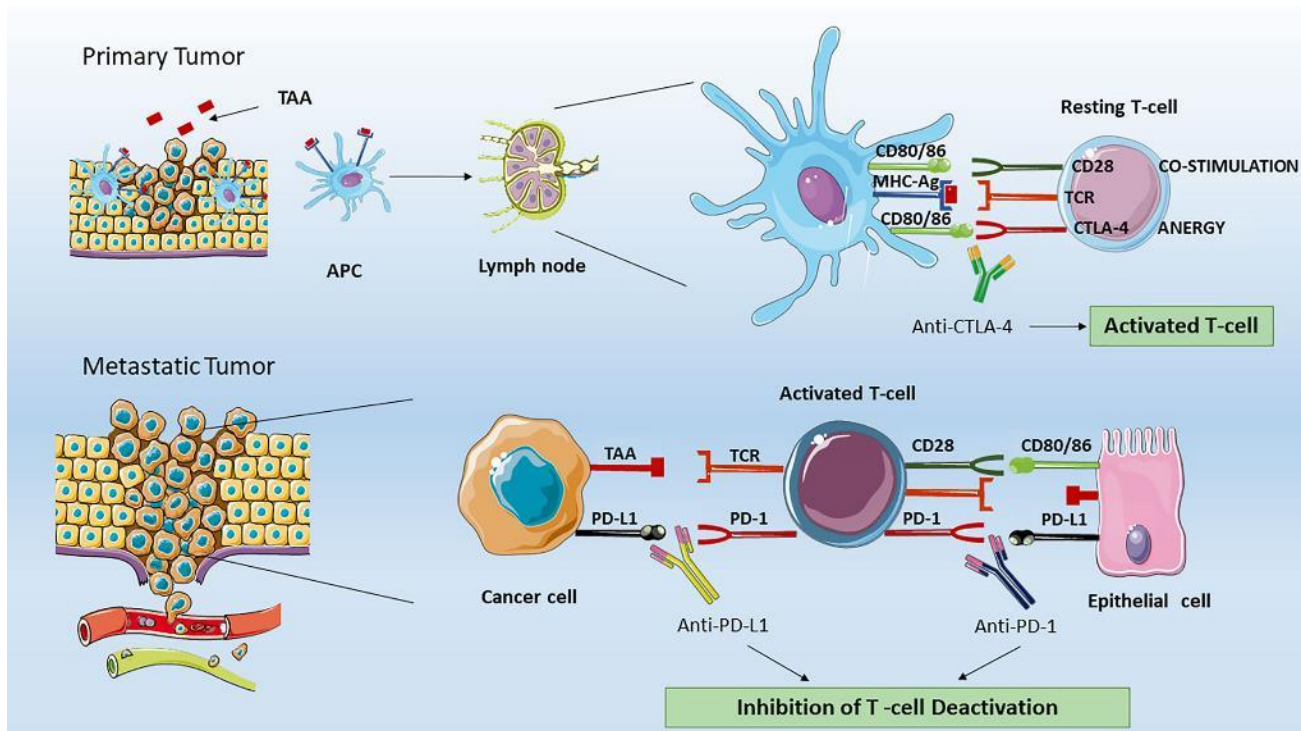
← PLK1 dependency



Immune surveillance in EB?



Immune Checkpoint Inhibition



Franzin et al., 2020 *Frontiers in Immunol.*

Immunotherapy dependent on CD8+ T-cells and IFN- γ response

HNSCC Poor Prognosis/ Response

IL6 High
PIK3CG High

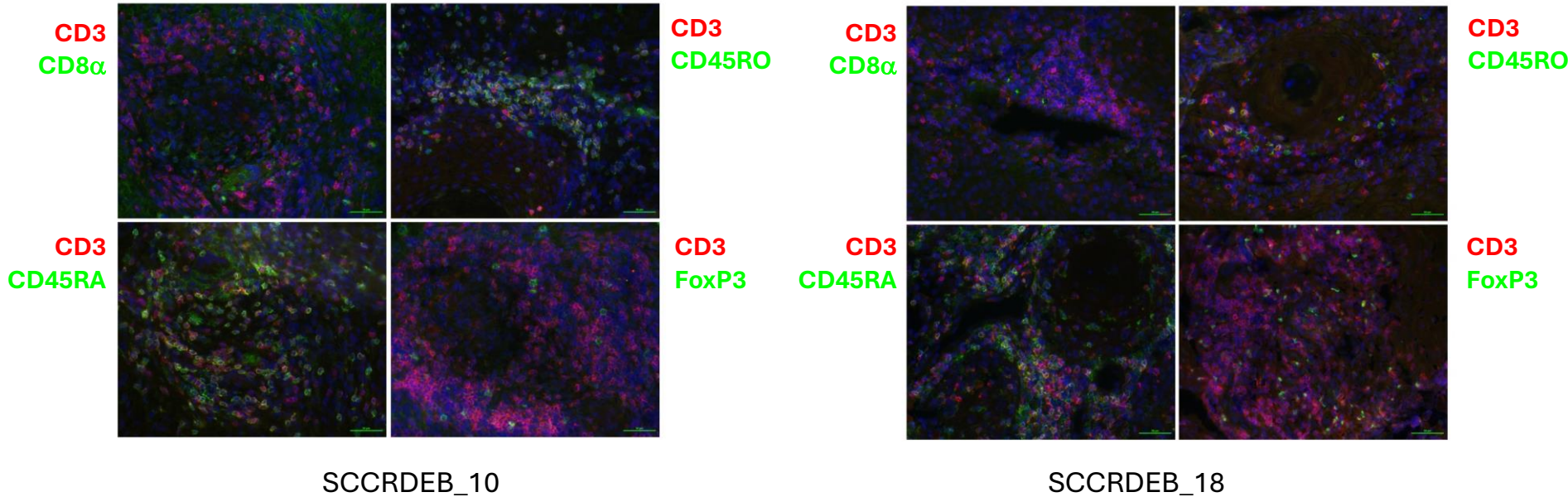
HNSCC Good Prognosis/ Response

IFNG High
CD8A High
IL12A High
IL12B High

RDEB SCC RNA-Seq

IL6 High ($\log_2 +6.3$)
PIK3CG High ($\log_2 +1.1$)
IFNG High ($\log_2 +4.7$)
CD8A High ($\log_2 +1.5$)

RDEB SCC harbor reduced CD8+ T-cells?



Immune dysregulation in RDEB cSCC?

Open Access Article

Immune Disregulation in Cutaneous Squamous Cell Carcinoma of Patients with Recessive Dystrophic Epidermolysis Bullosa: A Single Pilot Study

by Angela Filoni ^{1,2,*} , Gerolamo Cicco ¹ , Gerardo Cazzato ^{3,*} , Anna Bosco ¹ , Lucia Lospalluti ¹ , Marco Tucci ⁴ , Antonietta Cimmino ³ , Caterina Foti ¹ , Andrea Marzullo ³  and Domenico Bonamonte ¹ 

Experimental Dermatology 

RESEARCH ARTICLE |  Open Access | 

T-cell activation and bacterial infection in skin wounds of recessive dystrophic epidermolysis bullosa patients

Vitali Alexeev, Leonie Huitema, Taylor Phillips, Rodrigo Cepeda, Diego de los Cobos, Regina Isabella Matus Perez, Mauricio Salas-Garza, Oscar R. Fajardo-Ramirez, Franziska Ringpfeil, Jouni Uitto, Julio Cesar Salas-Alanis, Olga Igoucheva  ... See fewer authors 

First published: 27 May 2022 | <https://doi.org/10.1111/exd.14615>

Open Access Article

Epidermolysis-Bullosa-Associated Squamous Cell Carcinomas Support an Immunosuppressive Tumor Microenvironment: Prospects for Immunotherapy

by David Rafei-Shamsabadi ^{1,*} , Lena Scholten ¹ , Sisi Lu ^{1,2} , Daniele Castiglia ^{3,†} , Giovanna Zambruno ^{4,†} , Andreas Volz ⁵ , Andreas Arnold ⁵ , Mina Saleva ⁶ , Ludovic Martin ⁷ , Kristin Technau-Hafsi ¹ , Frank Meiss ¹ , Dagmar von Bubnoff ⁸  and Cristina Has ^{1,†} 

Open Access Article

Citrullinated Histone H3, a Marker for Neutrophil Extracellular Traps, Is Associated with Poor Prognosis in Cutaneous Squamous Cell Carcinoma Developing in Patients with Recessive Dystrophic Epidermolysis Bullosa

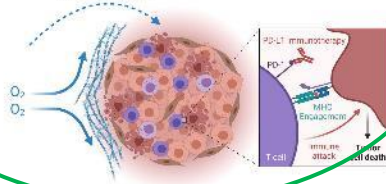
by H el ene Ragot ¹ , Sonia Gaucher ¹ , Mathilde Bonnet des Claustres ¹ , Justine Basset ¹ , Rose Boudan ², Maxime Battistella ³ , Emmanuelle Bourrat ² , Alain Hovnanian ^{1,4,*},   and Matthias Titeux ^{1,*},  

TME and Immune Checkpoint Inhibition

Good Outcome

Hot Tumor

Hypoxia upregulates PD-L1 on tumor



Immunosuppressed Tumor

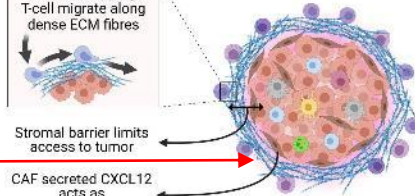
Immunosuppressive mechanisms

- Treg: IL-10, TGF β , IL-35, OX40, GITR, HVEM, CD28 & BTLA-1
- N2: NO, TNF α , Arginase 1, iNOS, IL-17
- M2 TAM: IL-10, TGF β , iNOS, Arginase 1
- MDSC: IL-10, TGF β , iNOS, Arginase 1, IDO, Peroxyrin
- DC, pDC: IL-10, TGF β , iNOS, Arginase 1, IDO
- CAF: TGF β , IDO, PDL2, VEGF, CXCL12, GM-CSF, CCL5

TGF β

Excluded Tumor

Immune trapping: T-cell migrate along dense ECM fibres

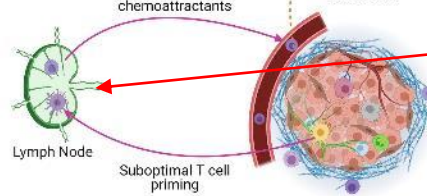


Fibrosis

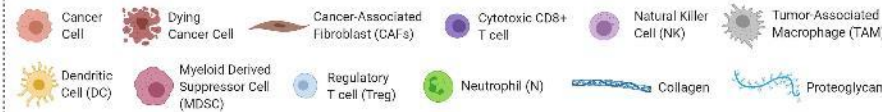
Cold Tumor

Impaired trafficking: Lack of chemoattractants

Endothelial cells downregulate adhesion molecules

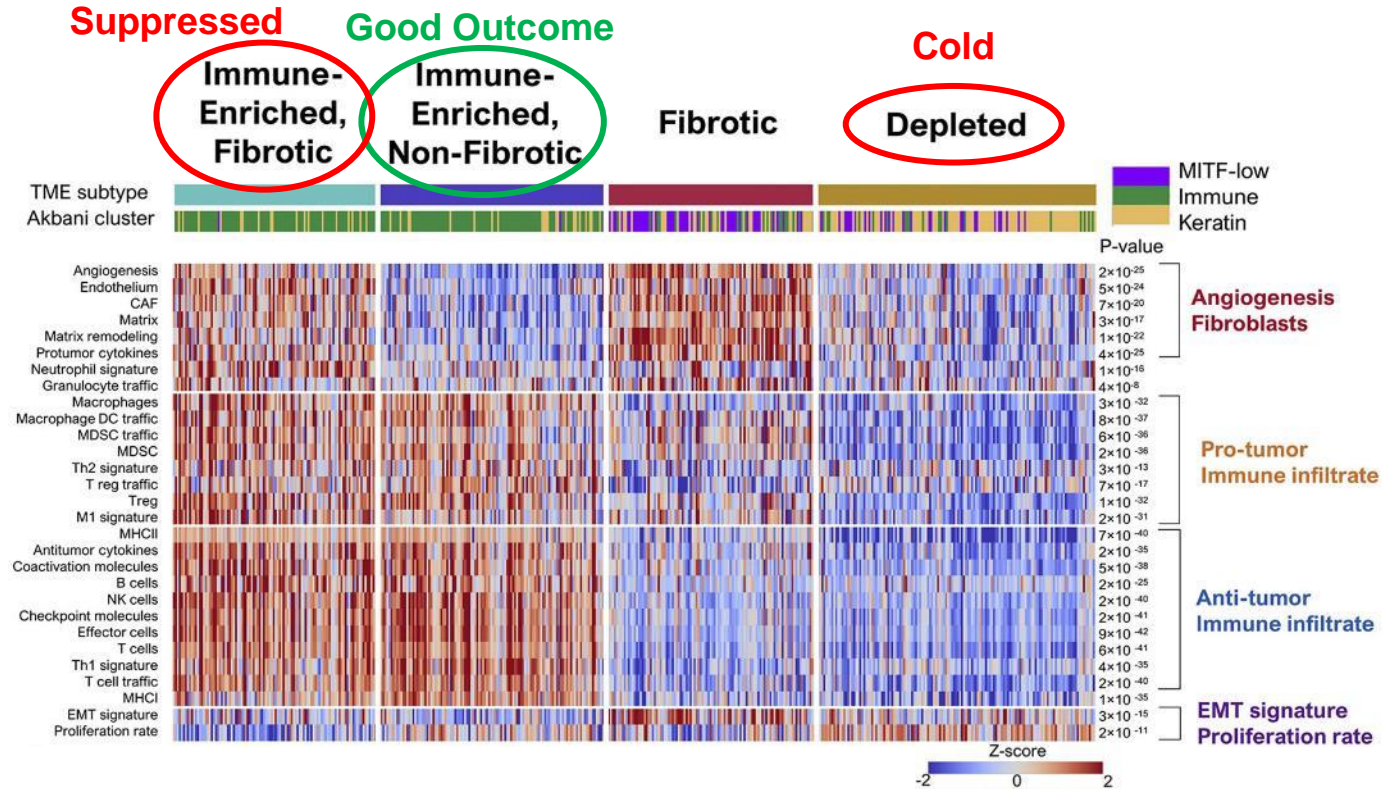


Impaired trafficking?
Nystrom et al., 2018 PNAS

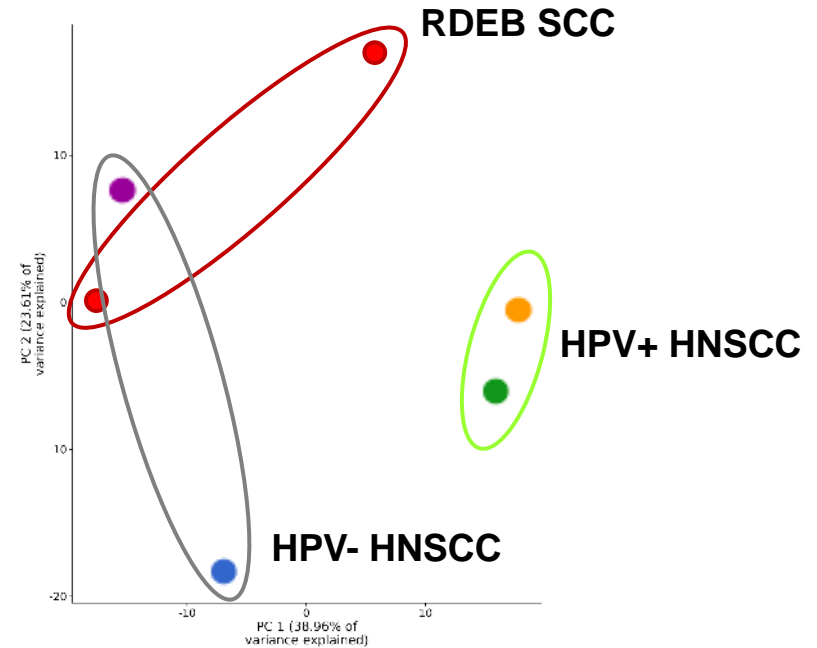
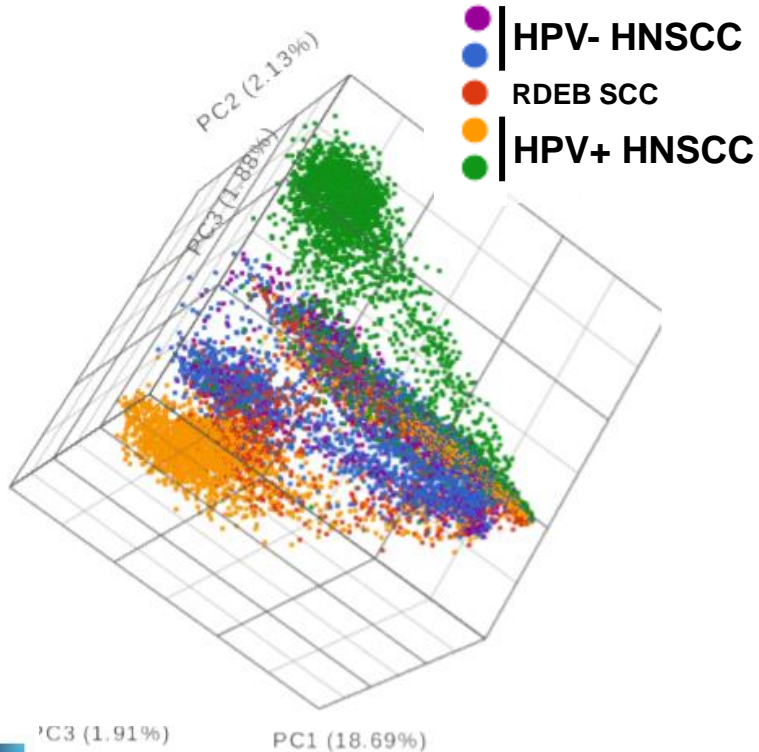


Hua Too., 2021 Adv. Drug Delivery Rev.

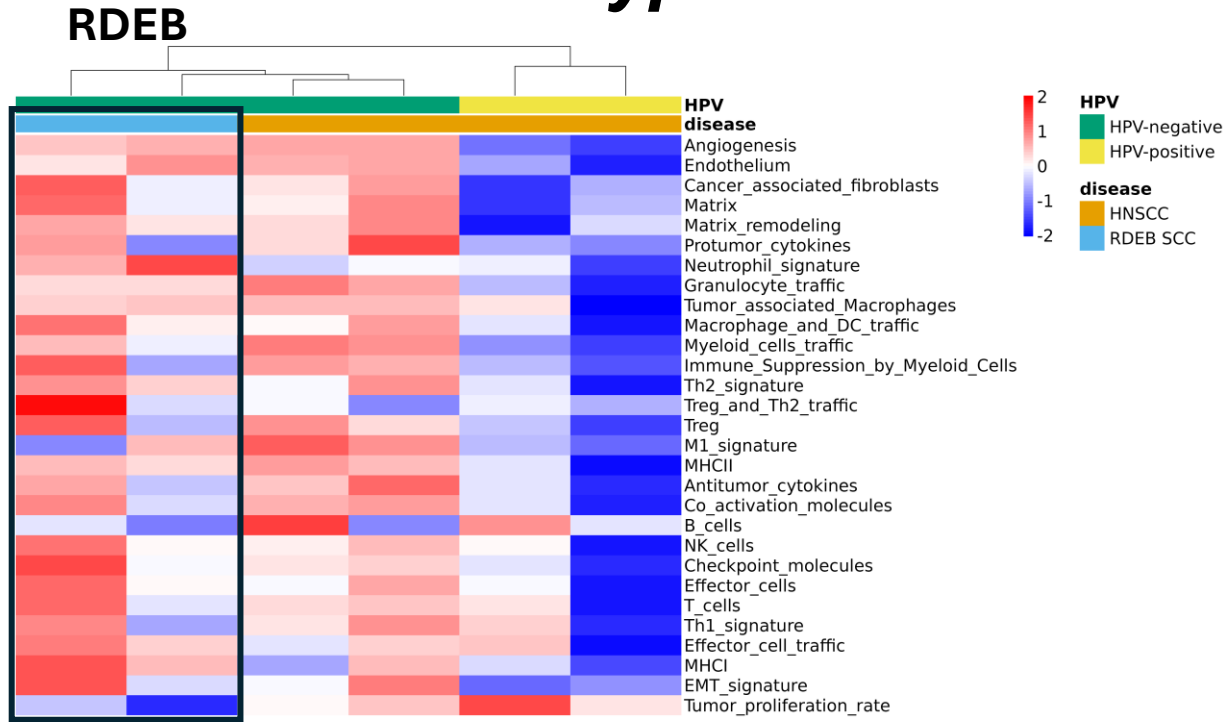
Tumor microenvironment classification



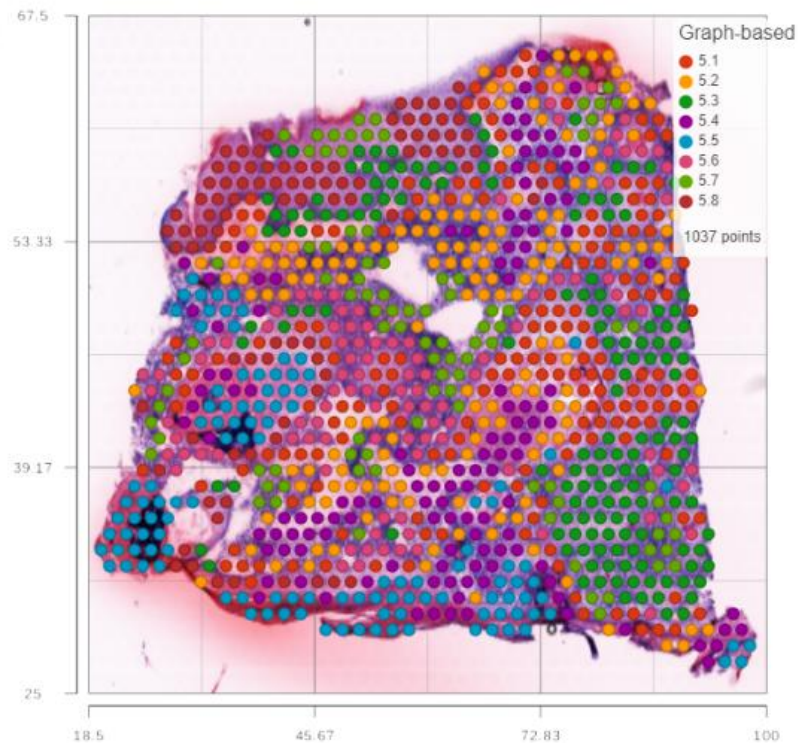
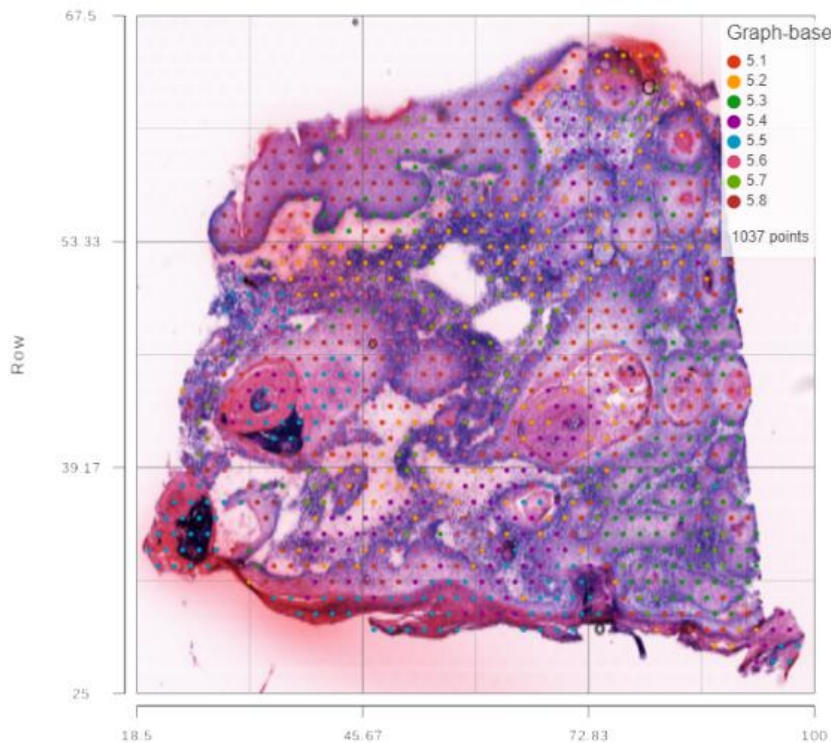
Single Cell Analysis of RDEB Cancer



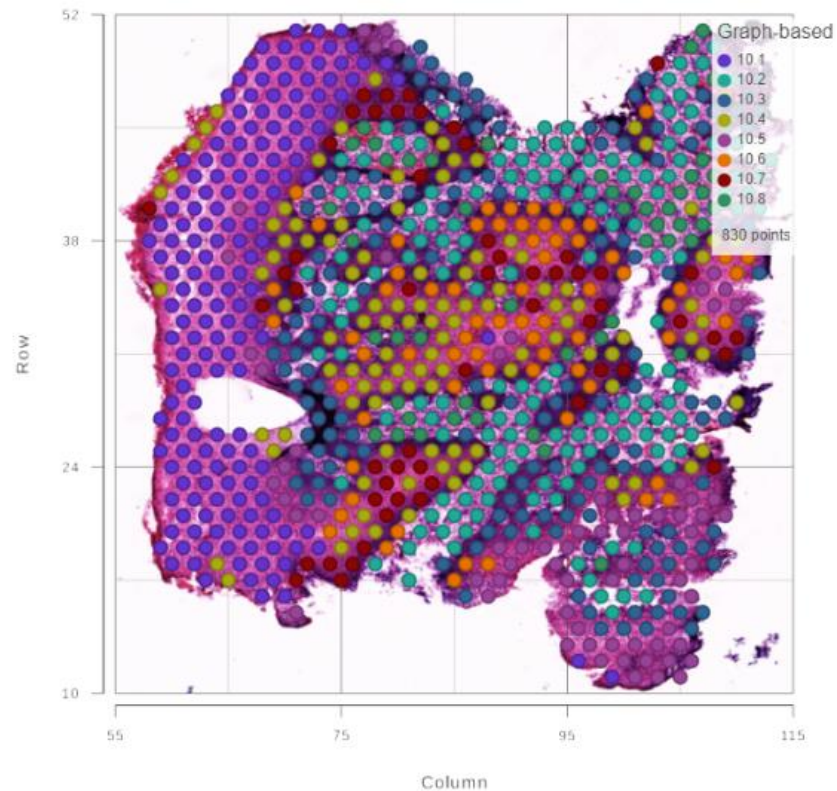
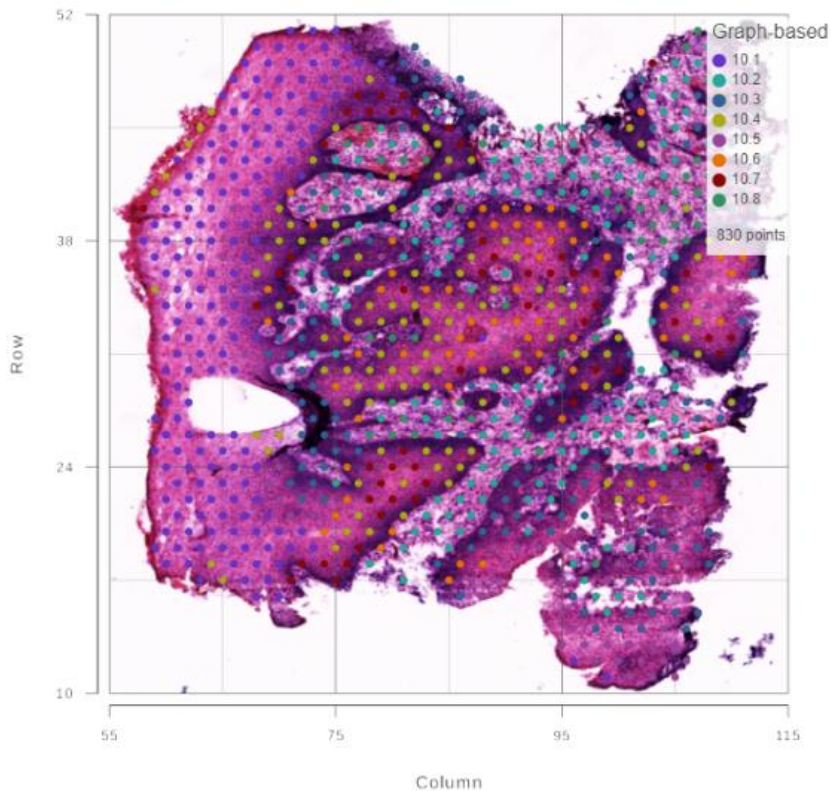
TME classification segregates single cell sample type



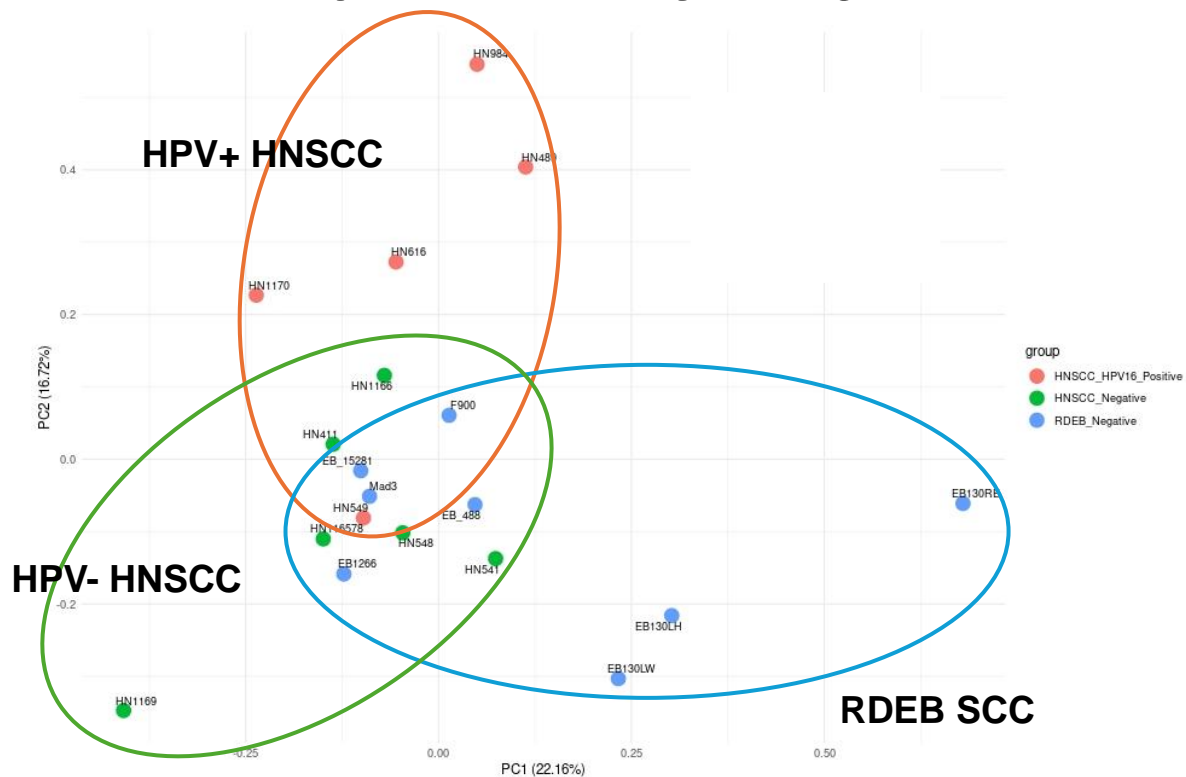
10X Visium Spatial Analysis of EB Cancer



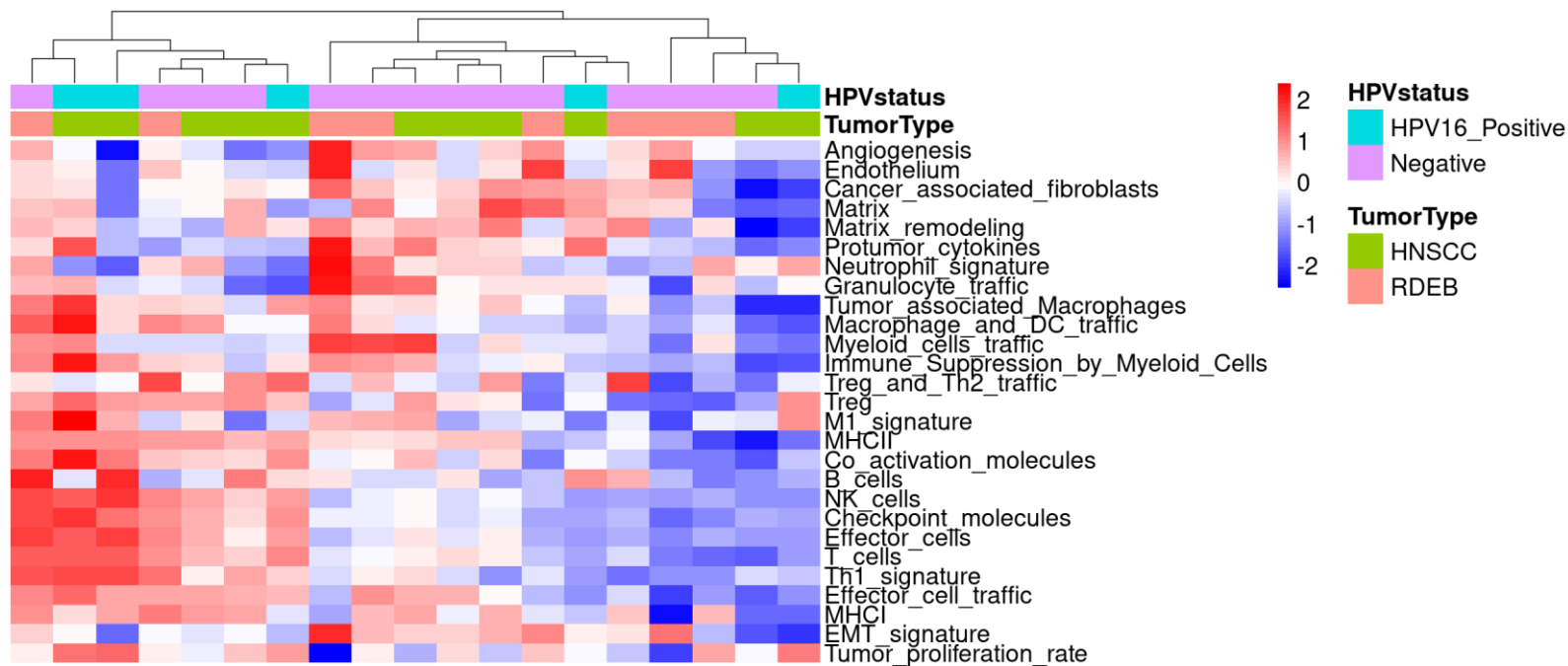
10X Visium Spatial Analysis of EB Cancer



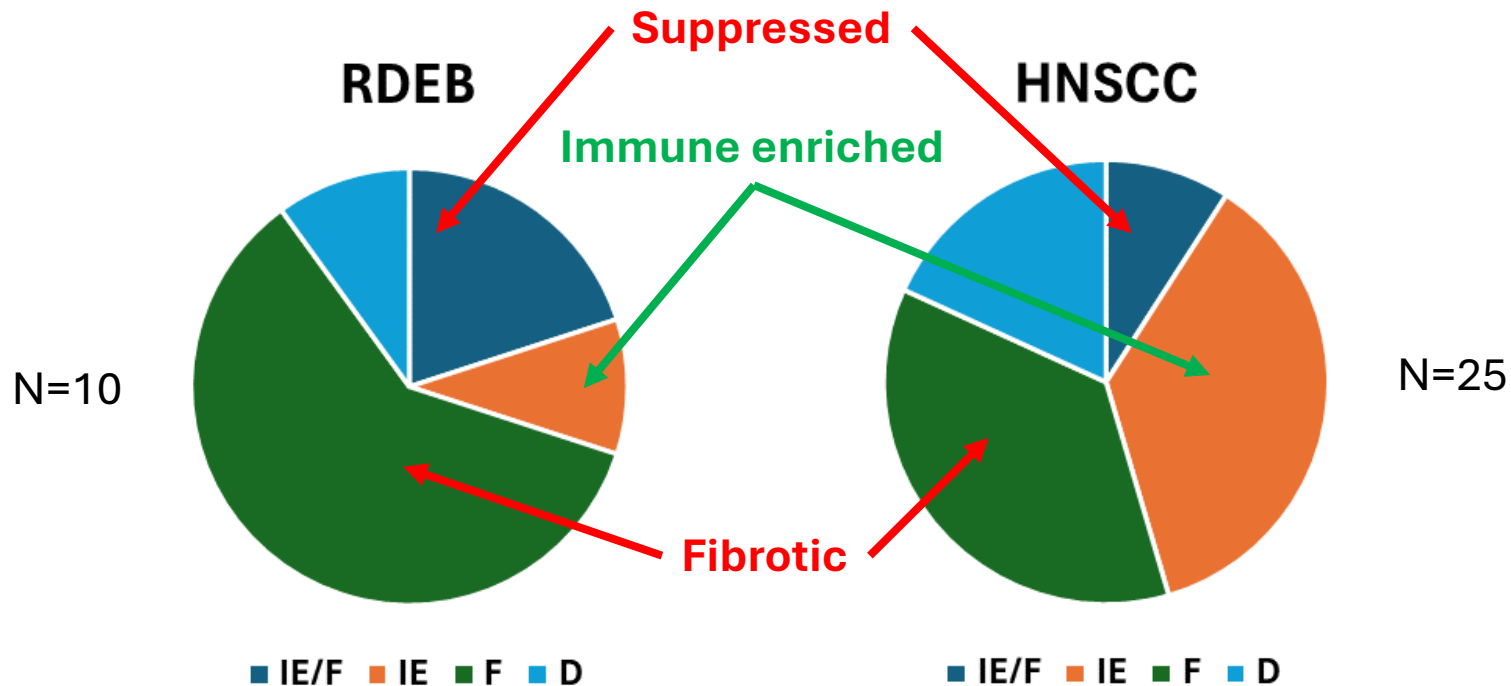
10X Visium Spatial Analysis of EB Cancer



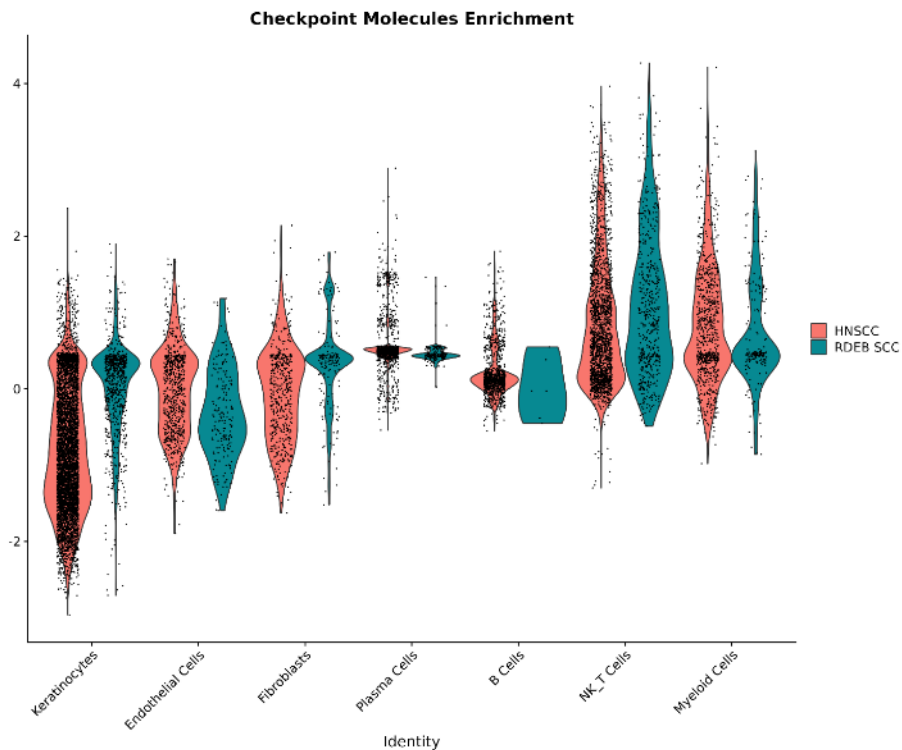
TME classification segregation of spatial data



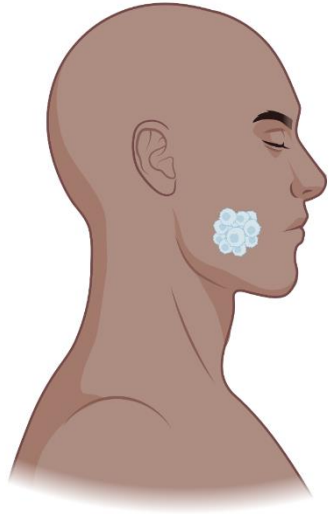
RDEB dominated by fibrotic TME and reduced Immune enriched TME



RDEB SCC immune checkpoint molecule signatures unremarkable



Window Trials



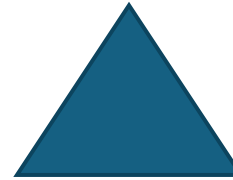
Head and neck SCC,
any stage



Biopsy,
diagnosis

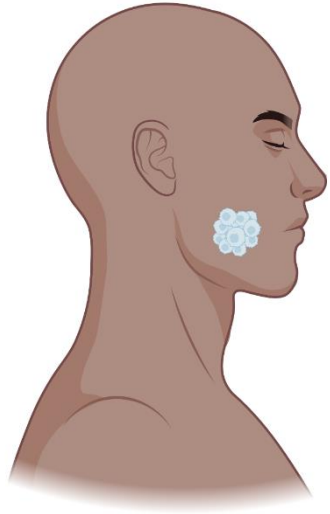


Tumor
resection



Window of opportunity

Window Trials



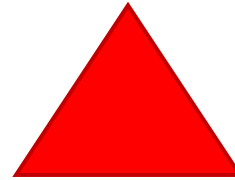
Head and neck SCC,
any stage



Biopsy,
diagnosis

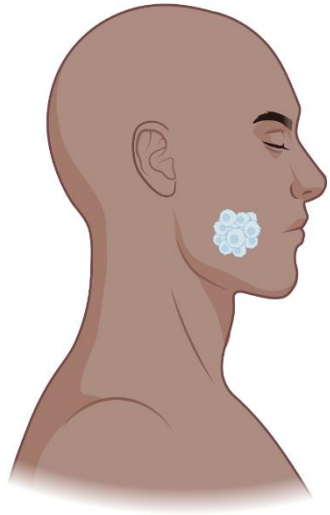


Tumor
resection

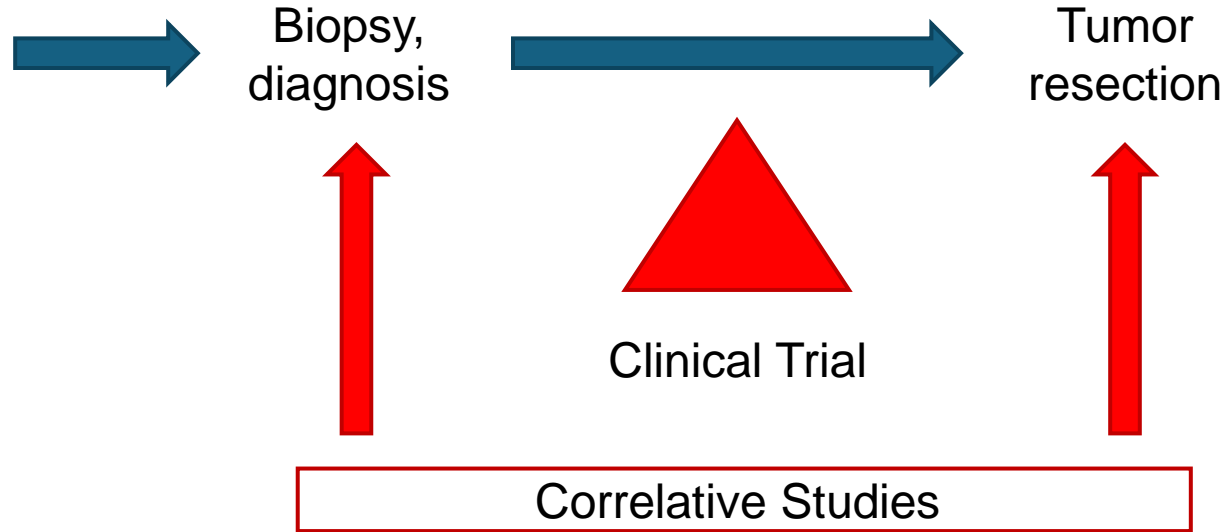


Clinical Trial

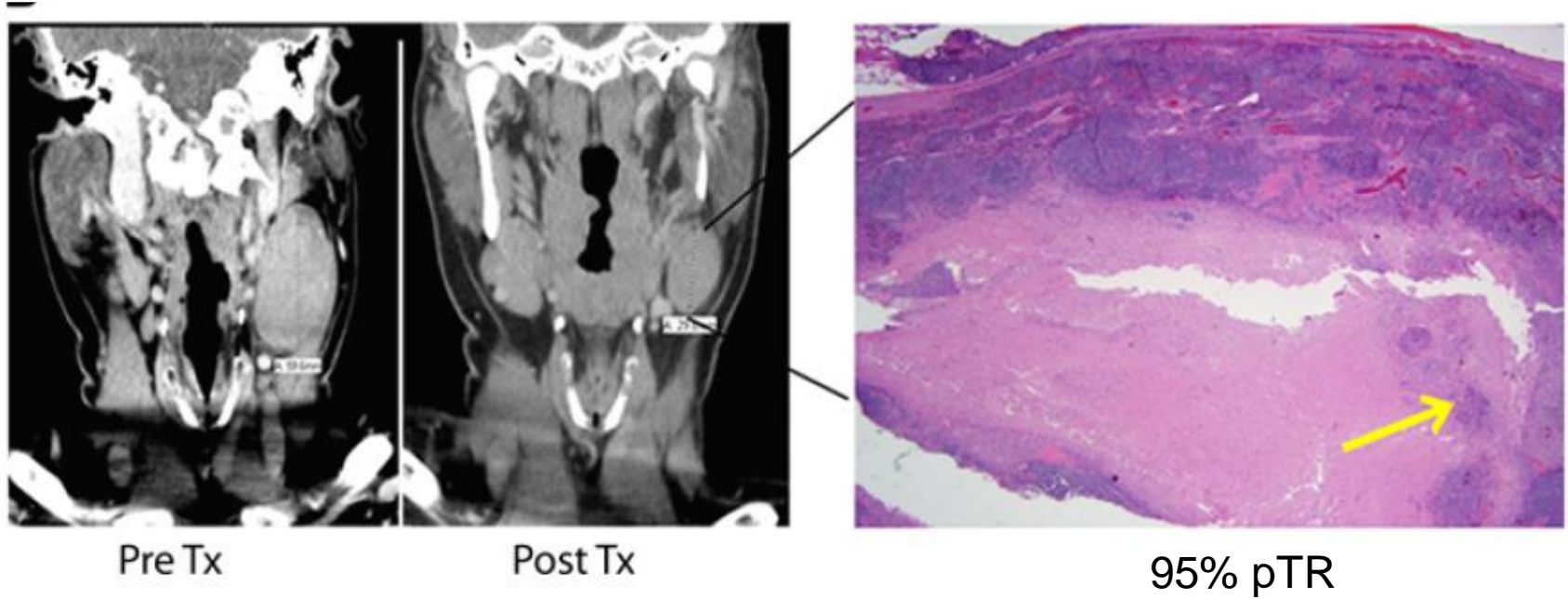
Window Trials



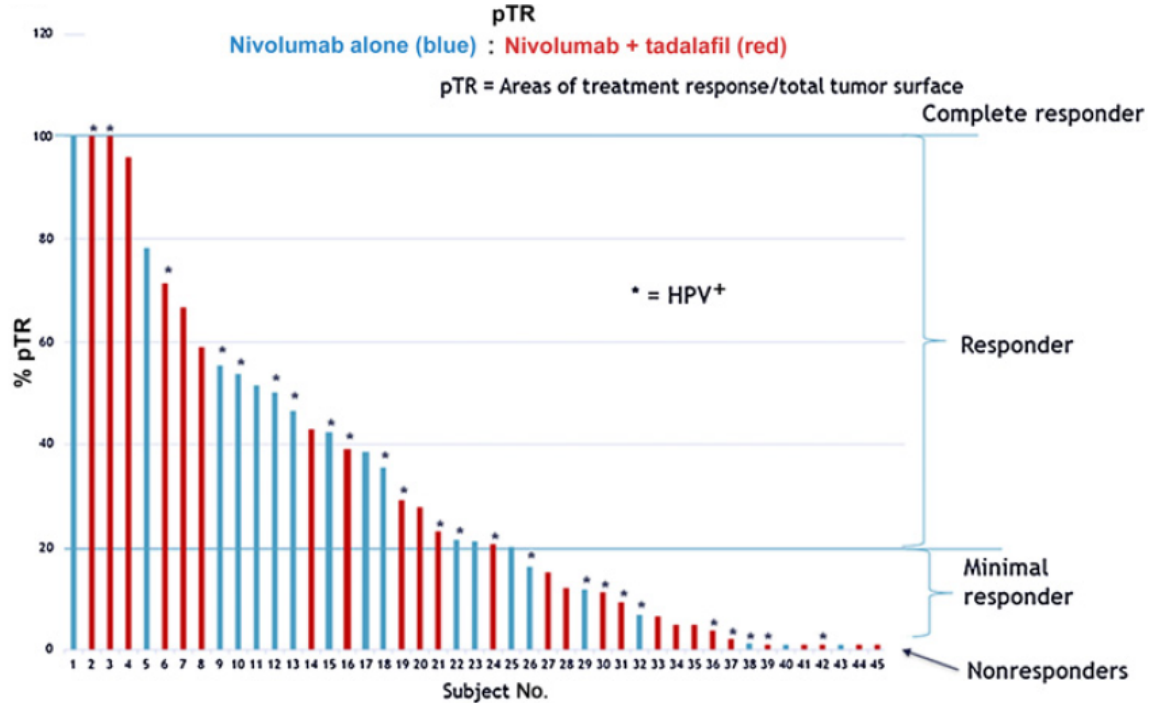
Head and neck SCC,
any stage



Pathological Treatment Response

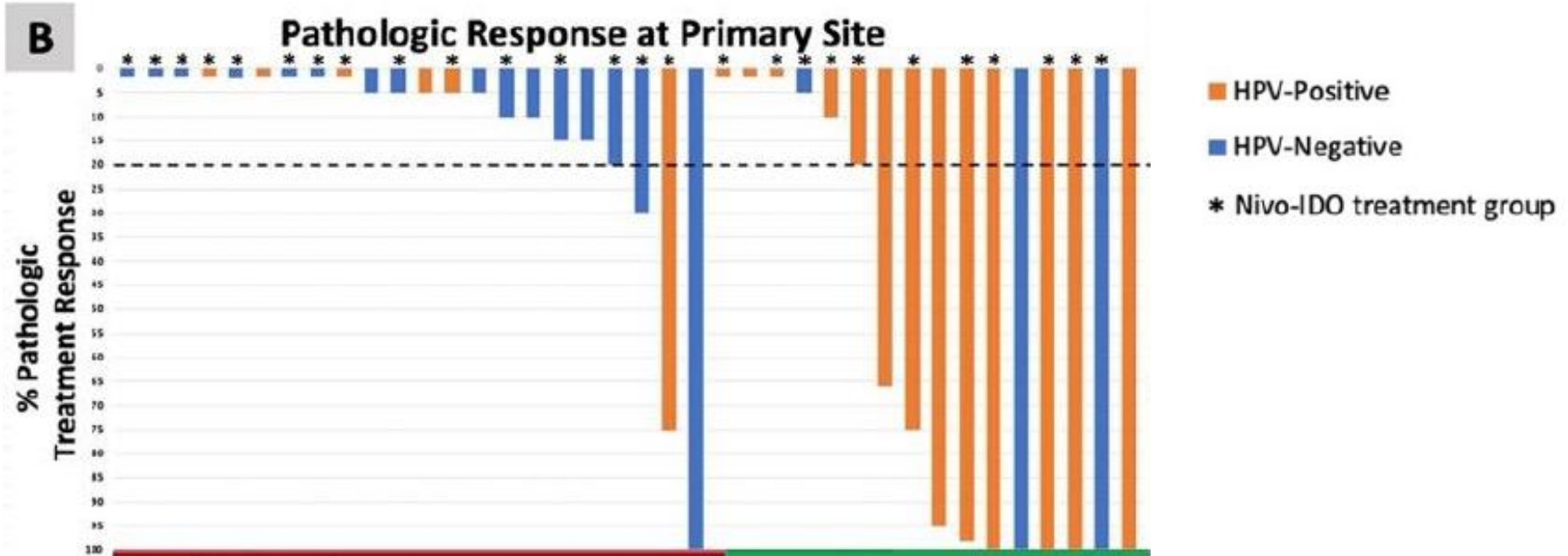


Window Trials



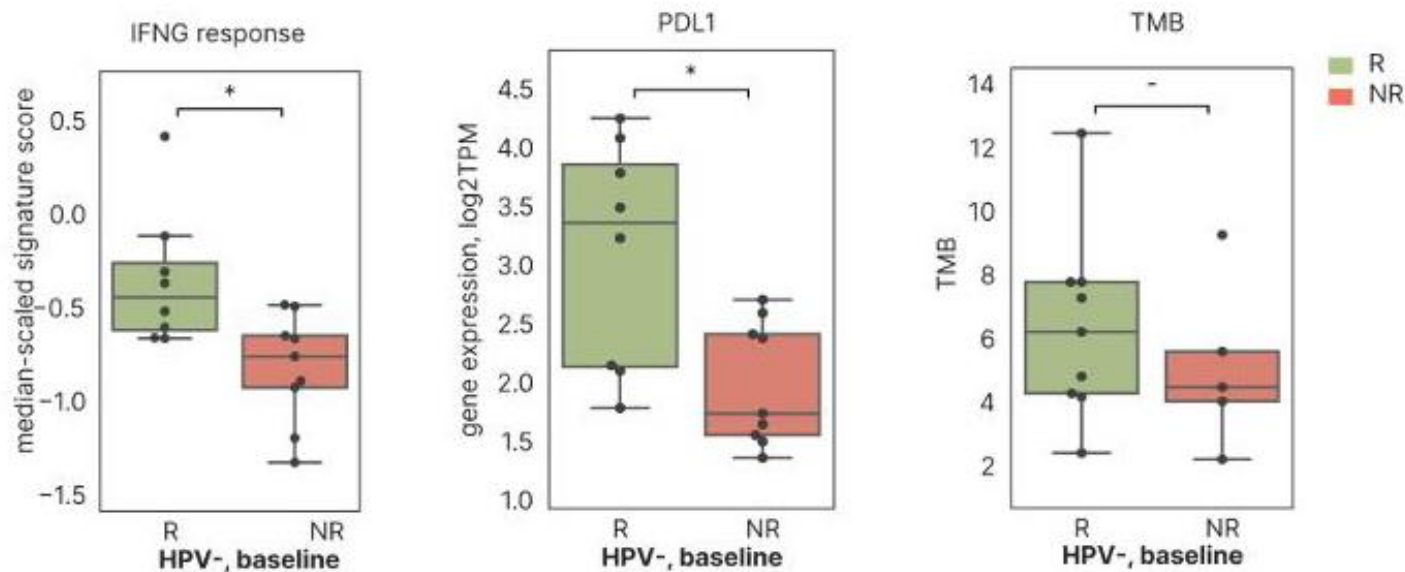
Luginbuhl et al, 2022

IDO inhibitor + Nivolumab



Mastrolonardo et al, *in press*

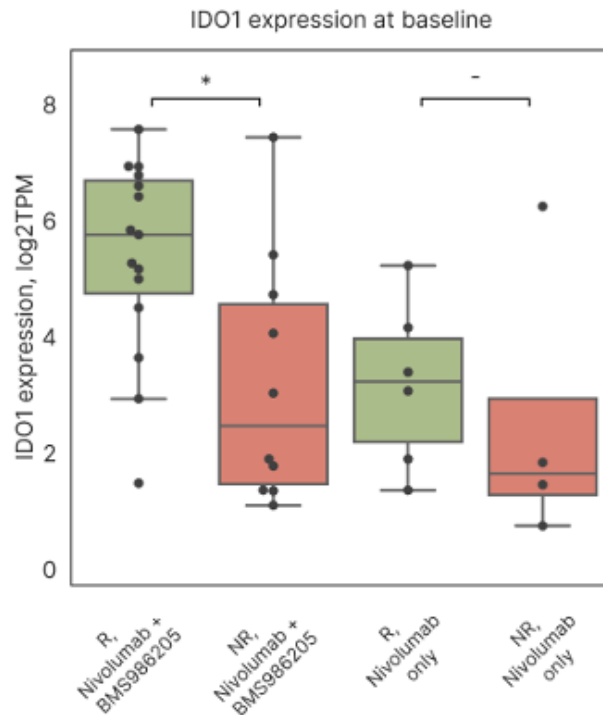
Can we predict response?



- ns, * p < 0.05, ** p < 0.01, *** p < 0.001

Mastrolonardo et al, *in press*

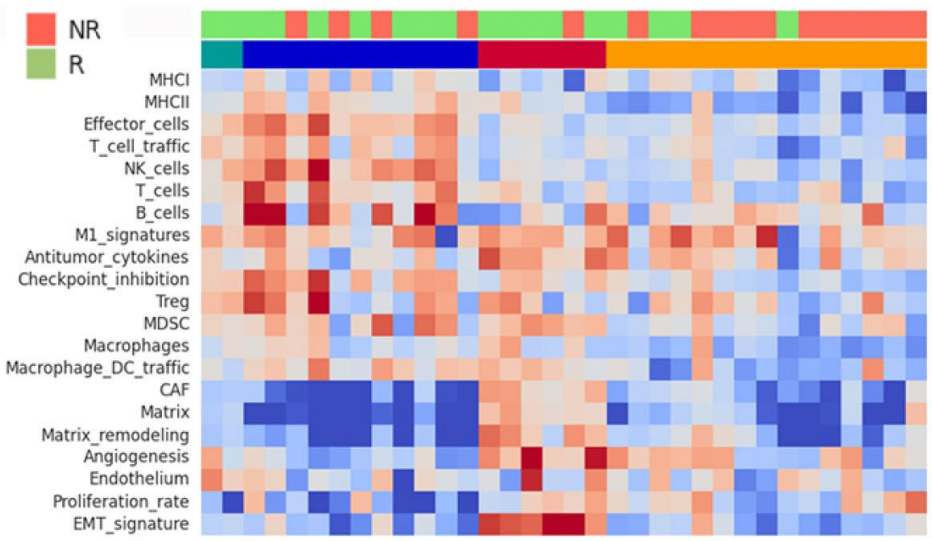
IDO1 levels predict response?



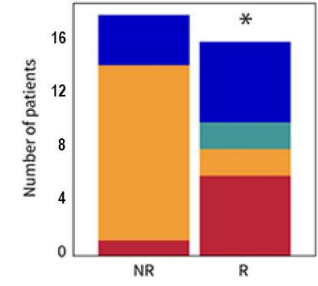
Mastrolonardo et al, *in press*

TME classification to predict response?

E



Overall Response



*Prediction of non-response: Immune desert vs all other phenotypes - $p=0.003$

Mastrolonardo et al, *in press*

Can we predict response to ICI from a blood draw?

Mastrolonardo et al, *in press*

Immunotype as a Marker of ICI Response

Cancer Cell

CellPress
OPEN ACCESS



Article

Comprehensive peripheral blood immunoprofiling reveals five immunotypes with immunotherapy response characteristics in patients with cancer

Daniyar Dyikanov,^{1,6} Aleksandr Zaitsev,^{1,6} Tatiana Vasileva,^{1,7} Iris Wang,^{1,7} Arseniy A. Sokolov,¹ Evgenii S. Bolshakov,¹ Alena Frank,¹ Polina Turova,¹ Olga Golubeva,¹ Anna Gantseva,¹ Anna Kamysheva,¹ Polina Shpudeiko,¹ Ilya Krauz,¹ Mary Abdou,¹ Madison Chasse,¹ Tori Conroy,¹ Nicholas R. Merriam,¹ Julia E. Alesse,¹ Noel English,¹ Boris Shpak,¹ Anna Shchetsova,¹ Evgenii Tikhonov,¹ Ivan Filatov,¹ Anastasia Radko,¹ Anastasiia Bolshakova,¹ Anastasia Kachalova,¹ Nika Lugovykh,¹ Andrey Bulahov,¹ Anastasiia Kilina,¹ Syimykh Asanbekov,¹ Irina Zheleznyak,¹ Pavel Skoptsov,¹ Evgenia Alekseeva,¹ Jennifer M. Johnson,² Joseph M. Curry,³ Alban J. Linnenbach,³ Andrew P. South,⁴ EnJun Yang,⁵ Kirill Morozov,¹ Anastasiya Terenteva,¹ Lira Nigmatullina,¹ Dmitry Fastovetz,¹ Anatoly Bobe,¹ Linda Balabanian,¹ Krystle Nomie,¹ Sheila T. Yong,¹ Christopher J.H. Davitt,¹ Alexander Ryabykh,¹ Olga Kudryashova,¹ Cagdas Tazearslan,¹ Alexander Bagaev,¹ Nathan Fowler,¹ Adam J. Luginbuhl,³ Ravshan I. Ataullakhanov,¹ and Michael F. Goldberg^{1,8,*}

¹BostonGene, Corp., Waltham, MA, USA

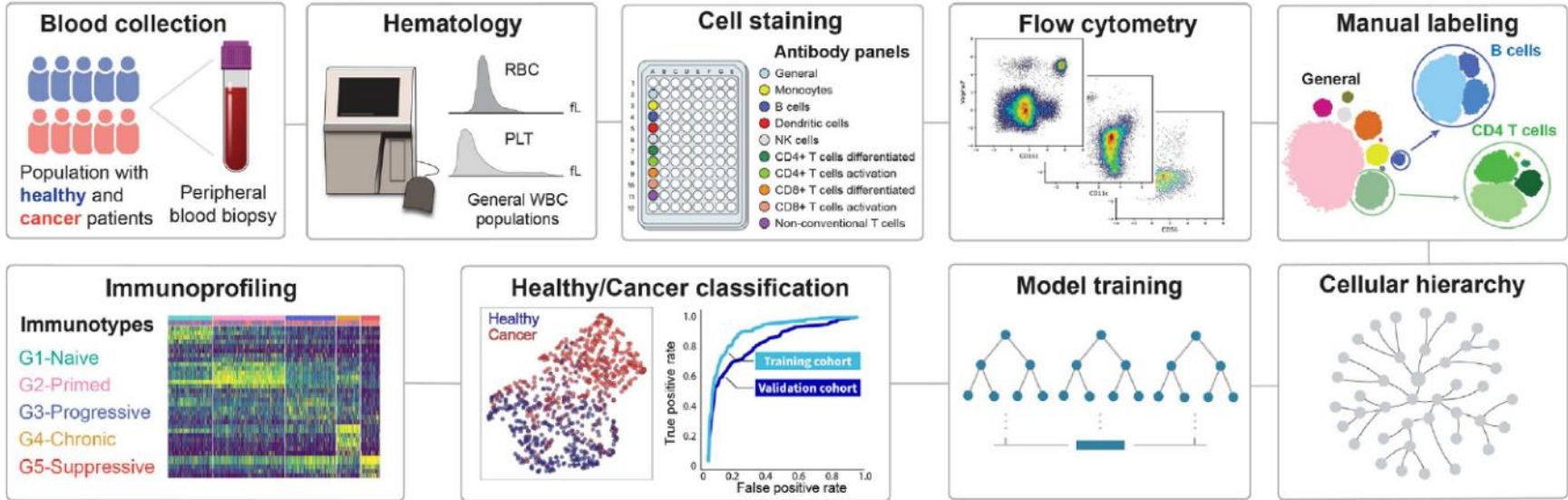
²Department of Medical Oncology, Thomas Jefferson University, Philadelphia, PA, USA

³Department of Otolaryngology Head and Neck Surgery, Thomas Jefferson University, Philadelphia, PA, USA

⁴Department of Pharmacology, Physiology, and Cancer Biology, Thomas Jefferson University, Philadelphia, PA, USA

⁵The Parker Institute for Cancer Immunotherapy, San Francisco, CA, USA

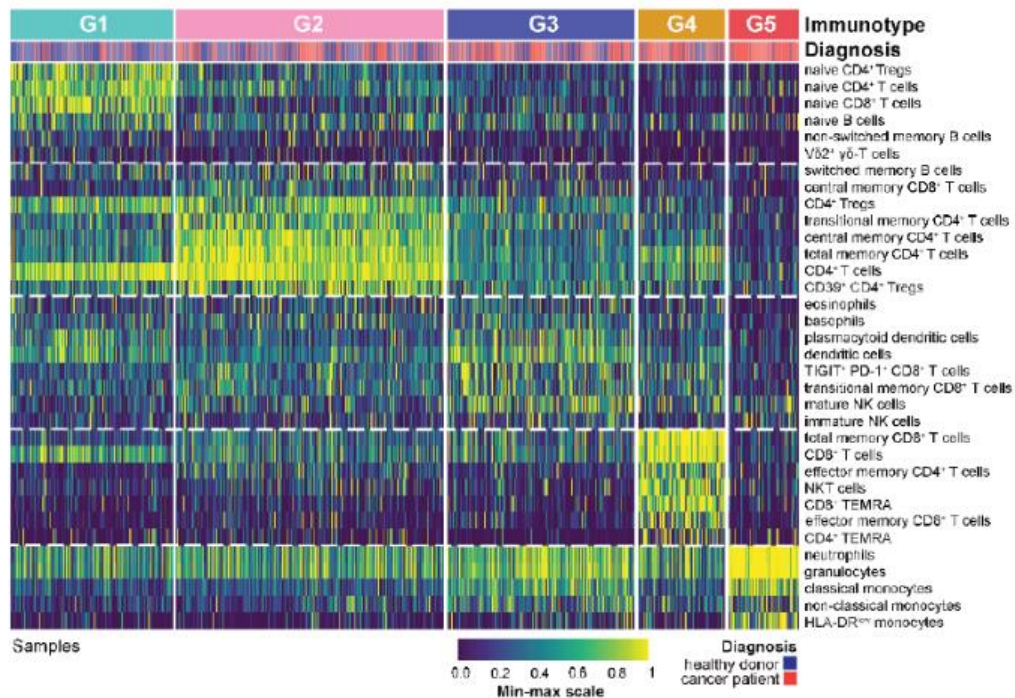
Immunoctype as a marker of ICI response



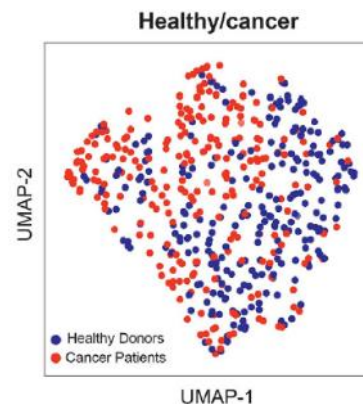
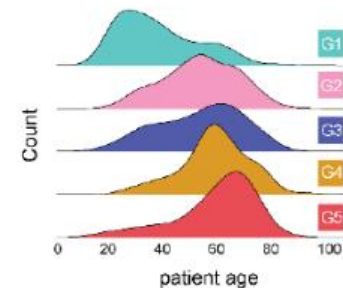
Dyikanov et al (2024). *Cancer Cell*.

Patients with specific immunotypes respond to ICI

A

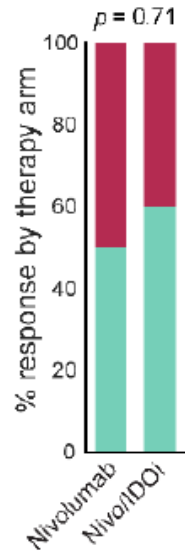
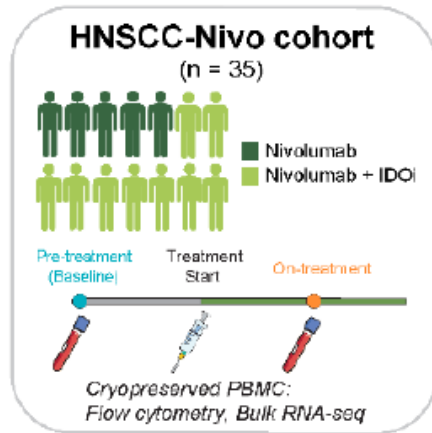


B



Patients with a “primed” immunotype respond to ICI (PD1 inhibition)

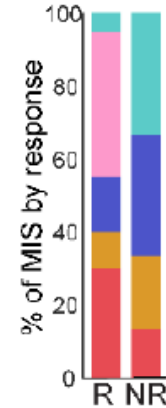
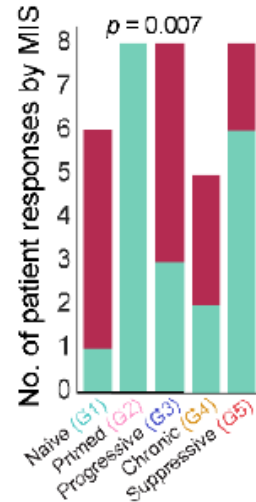
H



Non-responder (NR) ■
 Responder (R) ■

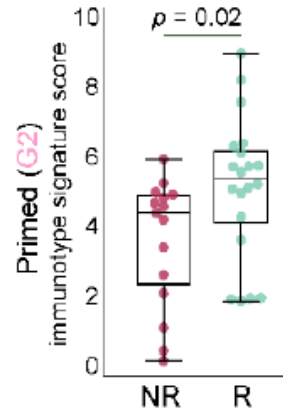
K

Pre-treatment



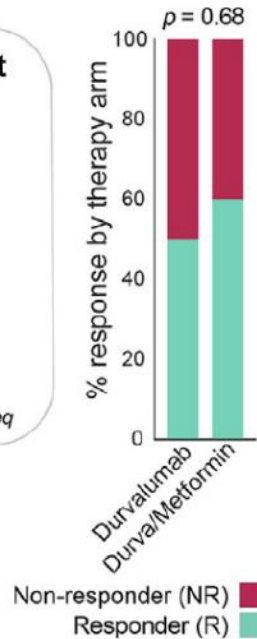
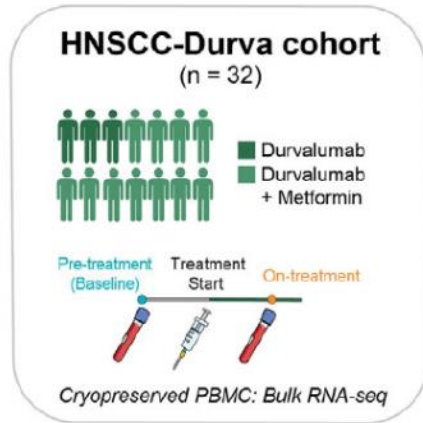
L

Pre-treatment

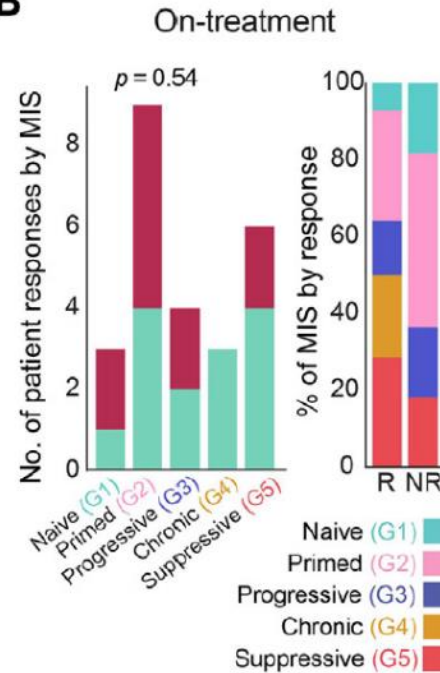


Patients with a “chronic” immunotype respond to ICI (PD-L1 inhibition)

A



B



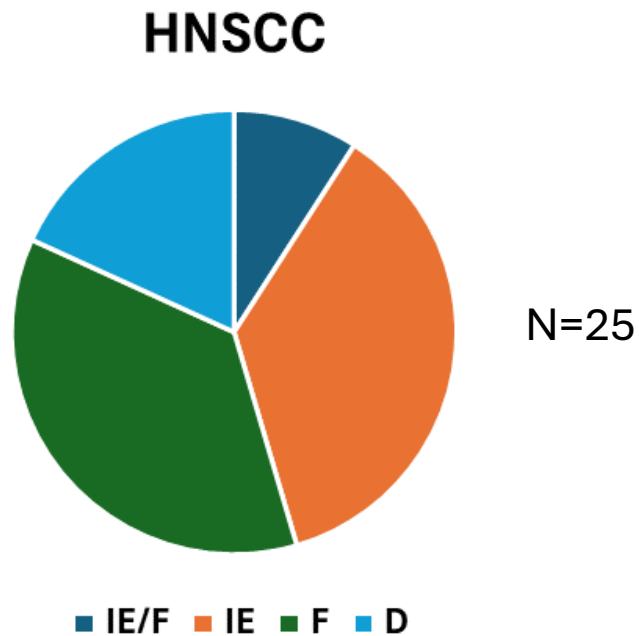
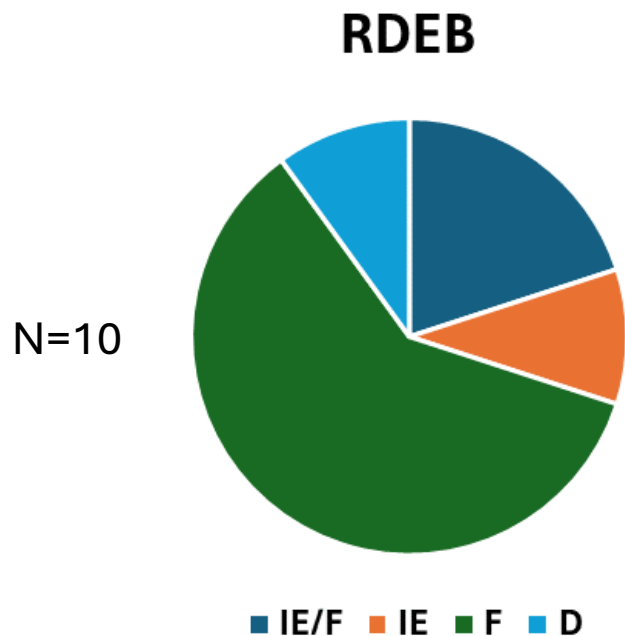
Window trials for predicting markers of ICI response

Analyzing pre and post treatment tumor tissue identifies markers enriched for response:

Tumors with an immune desert (“cold”) classification are less likely to respond to Nivo-IDO inhibition

Certain immunotypes from treatment naïve peripheral blood are more likely to respond to individual ICI

RDEB dominated by Fibrotic TME and reduced Immune Enriched TME



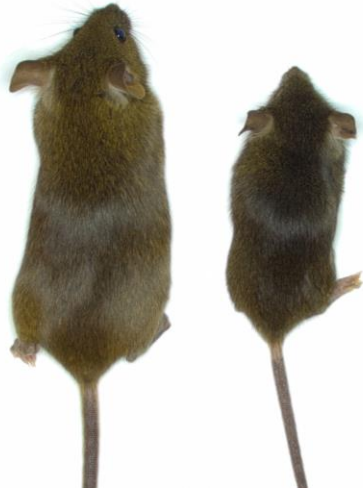
How can we predict response to ICI in a rare disease?

How can we predict response to ICI in a rare disease?



How can we predict response to ICI in EB?

Published OnlineFirst December 16, 2015; DOI: 10.1158/0008-5472.CAN-15-1348

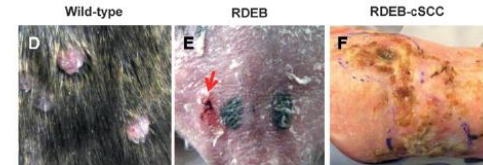
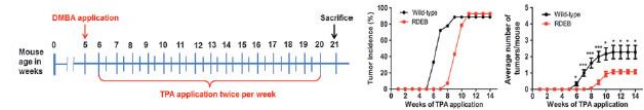


Tumor and Stem Cell Biology

Cancer Research

Injury-Driven Stiffening of the Dermis Expedites Skin Carcinoma Progression

Venugopal R. Mittapalli¹, Josef Madl^{2,3}, Stefanie Löffek¹, Dimitra Kirtsis¹, Johannes S. Kern¹, Winfried Römer^{2,3}, Alexander Nyström¹, and Leena Brückner-Tuderman^{1,3}



How can we model cancer in EB?



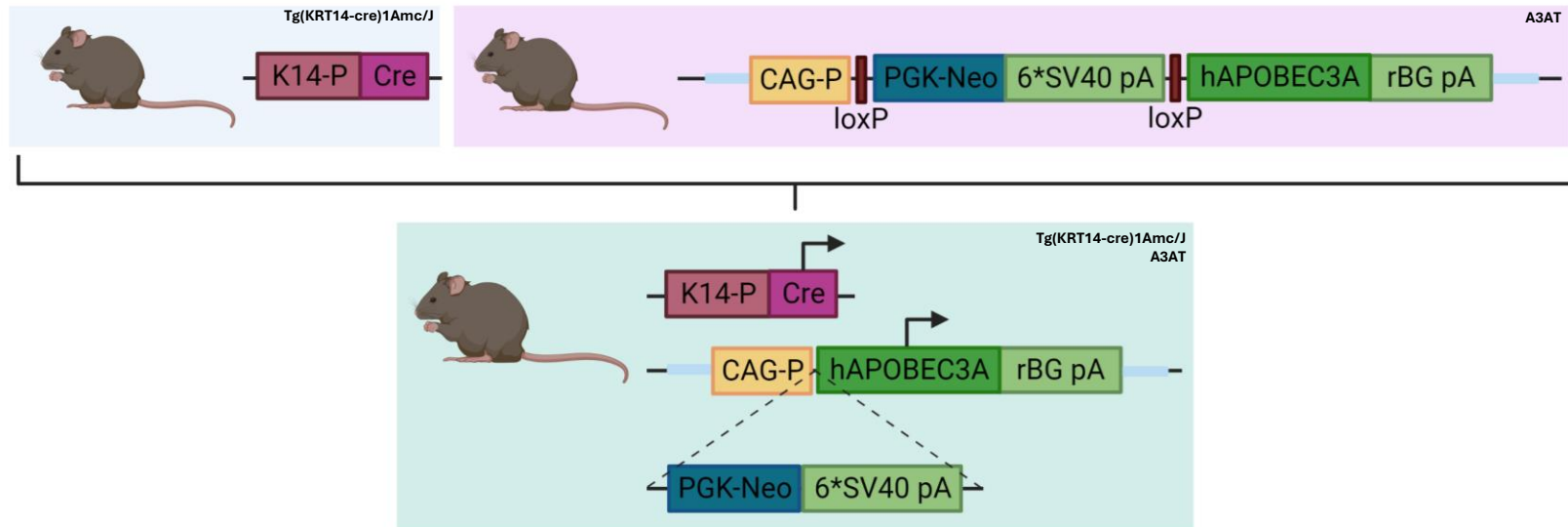
A need to improve survival

Expression of APOBEC enzymes

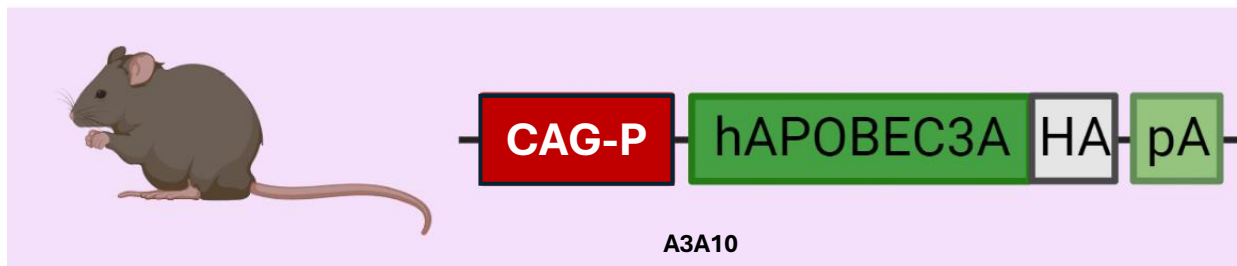
Model wound-induced cancer



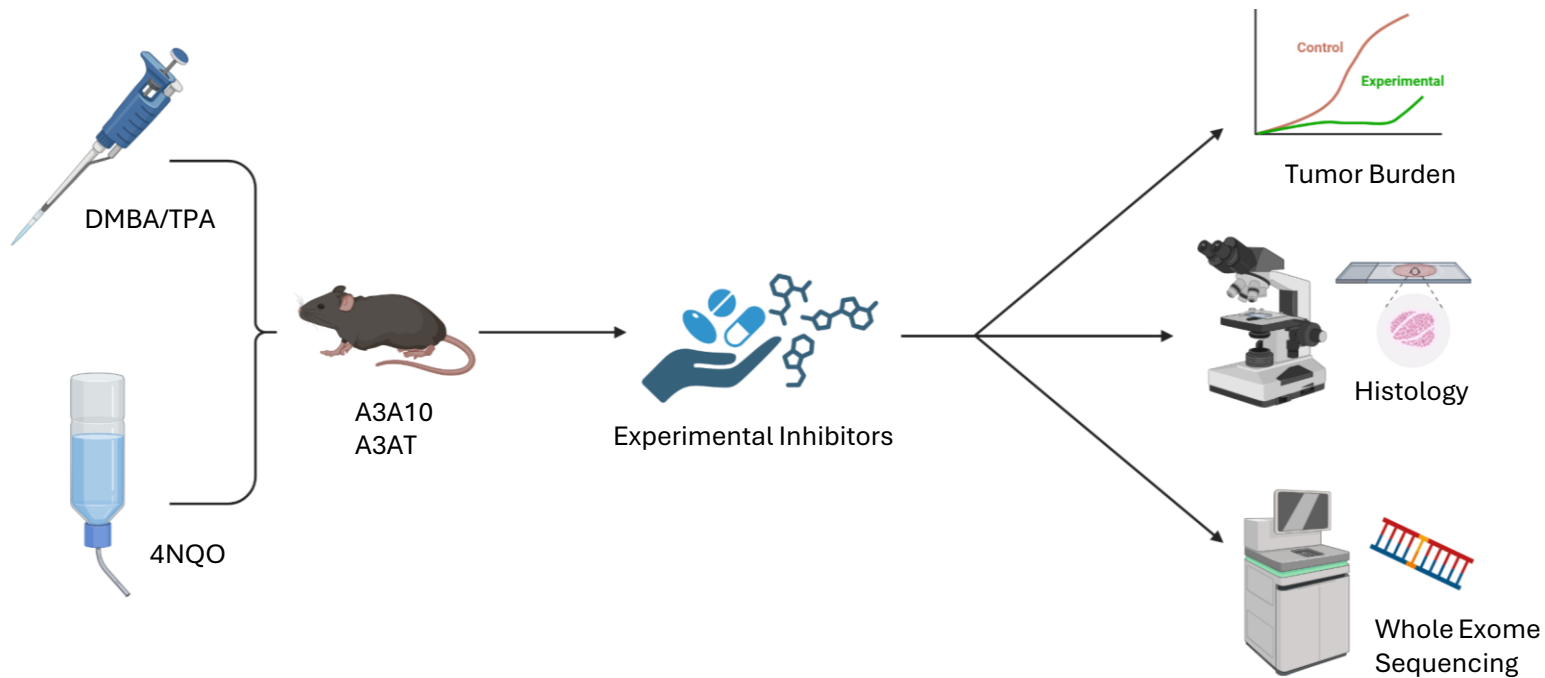
APOBEC Mouse Models: Targeted over expression, A3AT



APOBEC Mouse Models: Constitutive low level A3A, A3A10



Inhibiting A3A for cancer prevention?



A3A inhibitors

First-In-Class Small Molecule Inhibitors of the Single-Strand DNA Cytosine Deaminase APOBEC3G

Ming Li^{1,*}, Shivender M.D. Shandilya^{2,*}, Michael A. Carpenter¹, Anurag Rathore¹, William L. Brown¹, Angela L. Perkins³, Daniel A. Harki³, Jonathan Solberg⁴, Derek J. Hook⁴, Krishan K. Pandey⁵, Michael A. Parniak⁶, Jeffrey R. Johnson⁷, Nevan J. Krogan⁷, Mohan Somasundaran⁸, Akbar Ali⁸, Celia A. Schiffer⁸, and Reuben S. Harris^{1,#}

¹Department of Biochemistry, Molecular Biology & Biophysics, Institute for Molecular Virology, Center for Genome Engineering, 321 Church St. S.E., University of Minnesota, Minneapolis, Minnesota, USA 55455

²Department of Biochemistry & Molecular Pharmacology, University of Massachusetts Medical School, 364 Plantation Street, Worcester, Massachusetts, USA 01605

³Department of Medicinal Chemistry, University of Minnesota, 717 Delaware Ave, Minneapolis, Minnesota, USA 55414

⁴Department of Medicinal Chemistry, Institute for Therapeutics Discovery & Development, 717 Delaware Ave, University of Minnesota, Minneapolis, Minnesota, USA 55414

⁵Institute for Molecular Virology, Saint Louis University Health Sciences Center, 1100 South Grand Boulevard, St. Louis, Missouri, USA 63104

⁶Department of Microbiology and Molecular Genetics, University of Pittsburgh School of Medicine, 450 Technology Drive, Pittsburgh, Pennsylvania, USA 15219

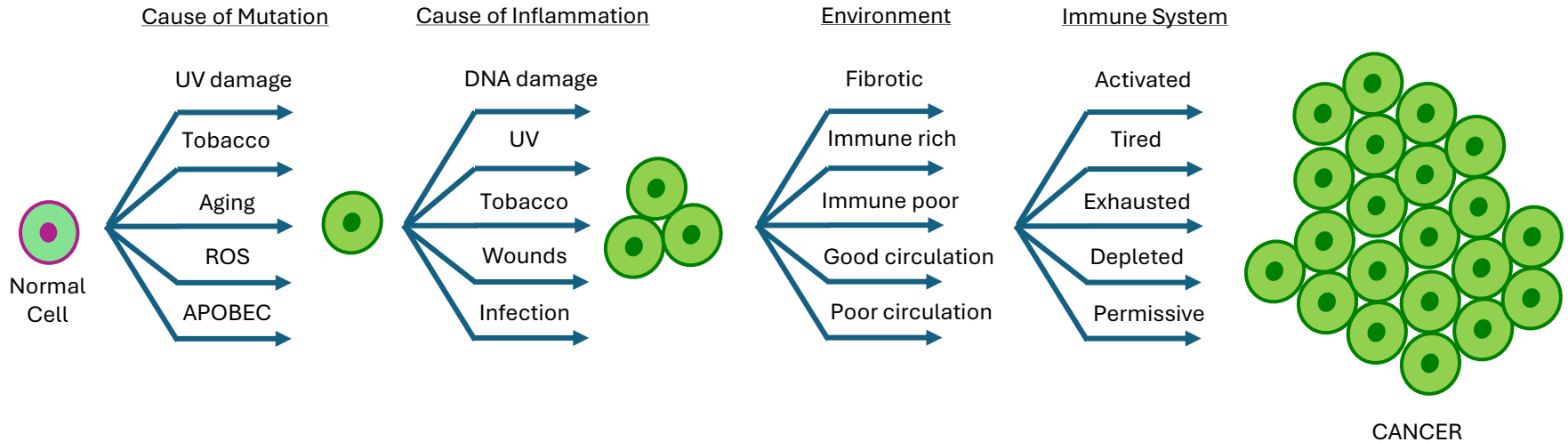
⁷Department of Cellular & Molecular Pharmacology, California Institute for Quantitative Biosciences, 600 16th Street, University of California-San Francisco, San Francisco, California, USA 94107

⁸Department of Pediatrics and Program in Molecular Medicine, University of Massachusetts Medical School, 364 Plantation Street, Worcester, Massachusetts, USA 01605

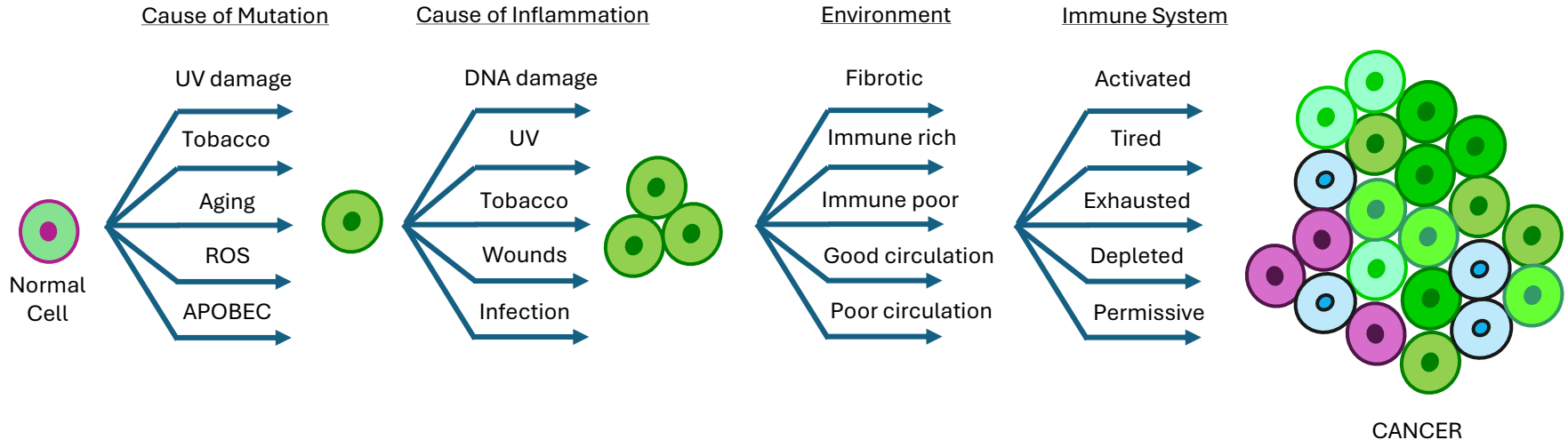
APOBEC3G inhibitor summary.

Entry	Common Name	PubChem CID	IC50 Values (µM)		
			A3A	A3G	UDG
MN1	Aurintricarboxylic acid	2259	0.03	0.49	15
MN2	R(-)-Aponorphine hydrochloride hemihydrate	107882	>200	1.3	>200
MN3	N-Acetylopropamine monohydrate	100526	>200	0.45	ND*
MN4	p-Benzquinone	4650	>200	0.17	ND
MN5	Caffeic acid	689043	>200	85	>200
MN6	4-Chloromercuribenzoic acid	1730	0.26	0.13	ND
MN7	Cephapirin sodium salt	23675312	12	7.5	ND
MN8	Dihydroxidine hydrochloride	11957519	>200	0.59	>200
MN9	S(-)-Carbidopa	34359	>200	5.3	ND
MN10	Dephostatin	5353574	150	0.43	>200
MN11	R(-)-N-Allylnorapomorphine hydrobromide	11857524	>200	2.9	ND
MN12	3,4-Dihydroxyphenylacetic acid	547	>200	1.9	>200
MN13	(±)-2-Amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene hydrobromide	11957526	>200	0.70	>200
MN14	R(-)-Propylnorapomorphine hydrochloride	11957529	>200	6.4	ND
MN15	(±)-SKF-38393 hydrochloride	147514	>200	27	>200
MN16	R(-)-2,10,11-Trihydroxyaporphine hydrobromide	11957531	>200	1.7	>200
MN17	R(-)-2,10,11-Trihydroxy-N-propylnoraporphine hydrobromide hydrate	10069059	>200	1.3	ND
MN18	Ebselen	3194	31	2.8	>200
MN19	5'-Guanidinonaltrindole di(trifluoroacetate) salt hydrate	9853099	0.42	6.4	>200
MN20	Iodoacetamide	3727	6.1	3.0	ND
MN21	Hydroquinone	785	>200	2.6	ND
MN22	1-(4-Hydroxybenzyl)imidazole-2-thio	3035523	>200	3.5	>200
MN23	6-Hydroxy-DL-DOPA	107794	0.30	4.0	>200
MN24	Hispidin	5353671	>200	2.0	>200
MN25	(1R,2S)-(-)-Ephedrine	9294	54	1.3	ND
MN26	Aurothioglucose hydrate	6194	>200	0.36	>200
MN27	Myricetin	5281672	0.60	3.4	>200

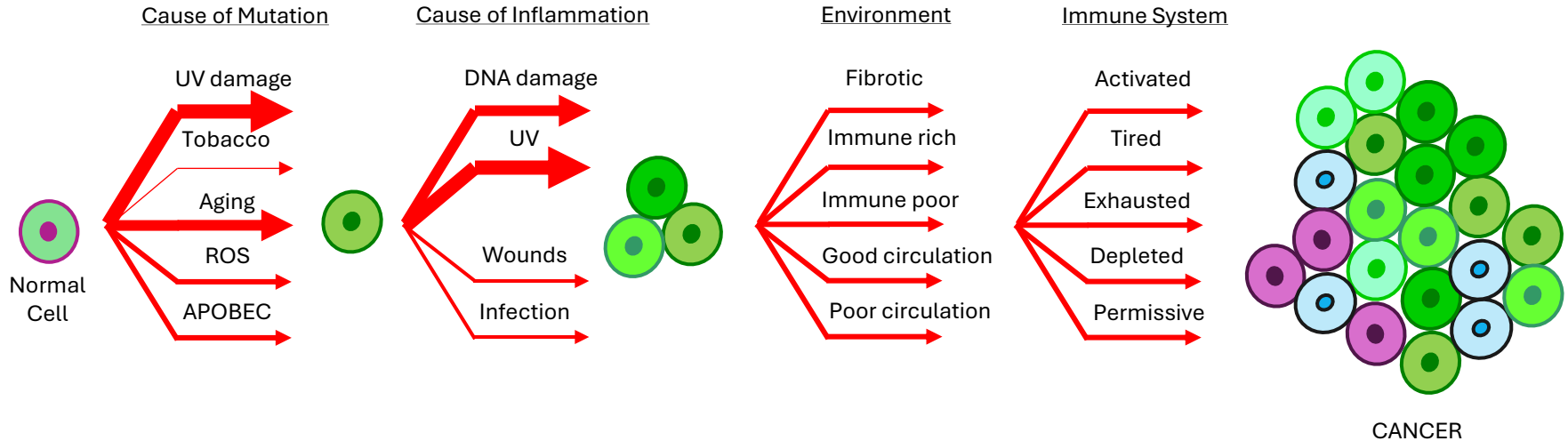
Many paths can lead to cancer



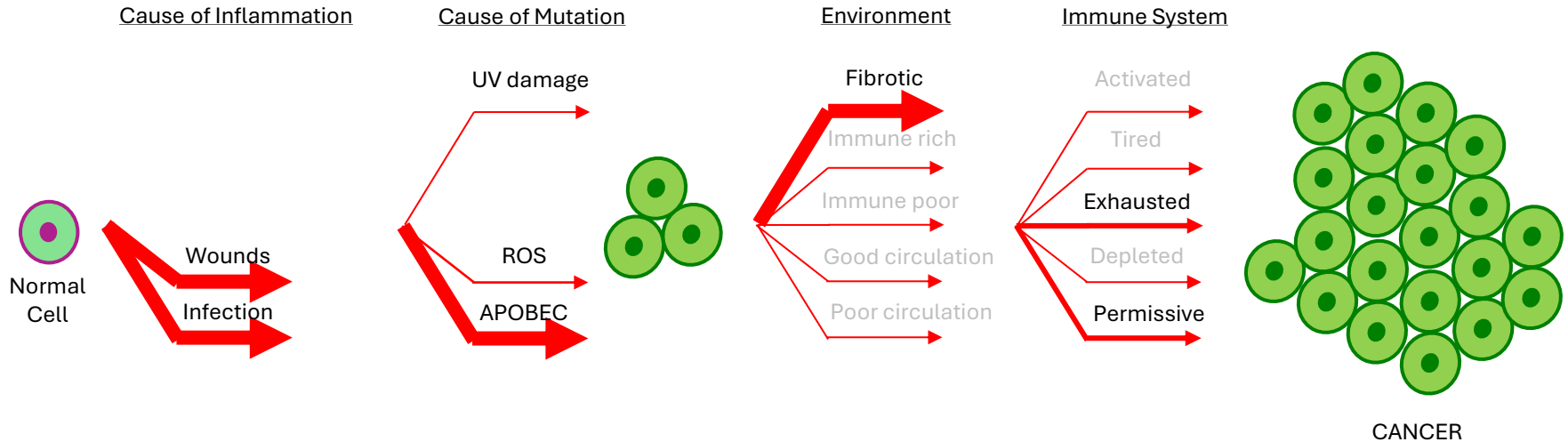
Many paths can lead to cancer



Non-EB Cutaneous SCC



EB SCC develops from fewer paths



Conclusions – where are we?

EB SCC arise in a permissive environment leading to homogeneous primary tumors with a mitotic trajectory (driven by PLK1)

Immune Checkpoint Inhibition is a viable therapy for EB SCC but not all patients respond

Further work to determine the tumor microenvironment and patient immunotypes is needed to fully understand EB SCC

Acknowledgements

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Kathryn Sun

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Alban Linnenbach

Joseph Curry

Adam Luginbuhl

Suhao Han

Paolo Fortina

Salzburg

Martin Laimer

Johann Bauer

Christina Guttmann-Gruber

Josefina Pinon Hofbauer

Missouri

Jon Dyer

Freiberg

Cristina Has

London

Jemma Mellerio

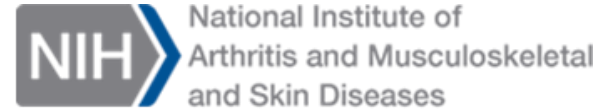
John McGrath

Groningen

Marieke Bolling



Award No. 1R01CA244522-01A1: Tissue Damage-Driven Squamous Cell Carcinoma



Award No. 1R01AR082944-01A1: The role of collagen VII in extracellular matrix secretion



EB RESEARCH PARTNERSHIP

