
2019
21-23 JUNE
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SUPPORTIVE CARE
MAKES EXCELLENT
CANCER CARE POSSIBLE
Pathogenesis: Oral vs Gastrointestinal
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Conflict of Interest Disclosure

Joanne Bowen, PhD

- Contracted Research
  - Puma Biotechnology
  - Pfizer Pharmaceuticals
  - AstraZeneca
  - Helsinn Healthcare
  - Entera Health Inc.

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Goals of this talk

- **Compare and contrast oral v GI mucositis**
  - Common, overlapping, and unique features
- **Highlight new insights from review**
  - Emerging targets and technologies

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Mucositis Guidelines

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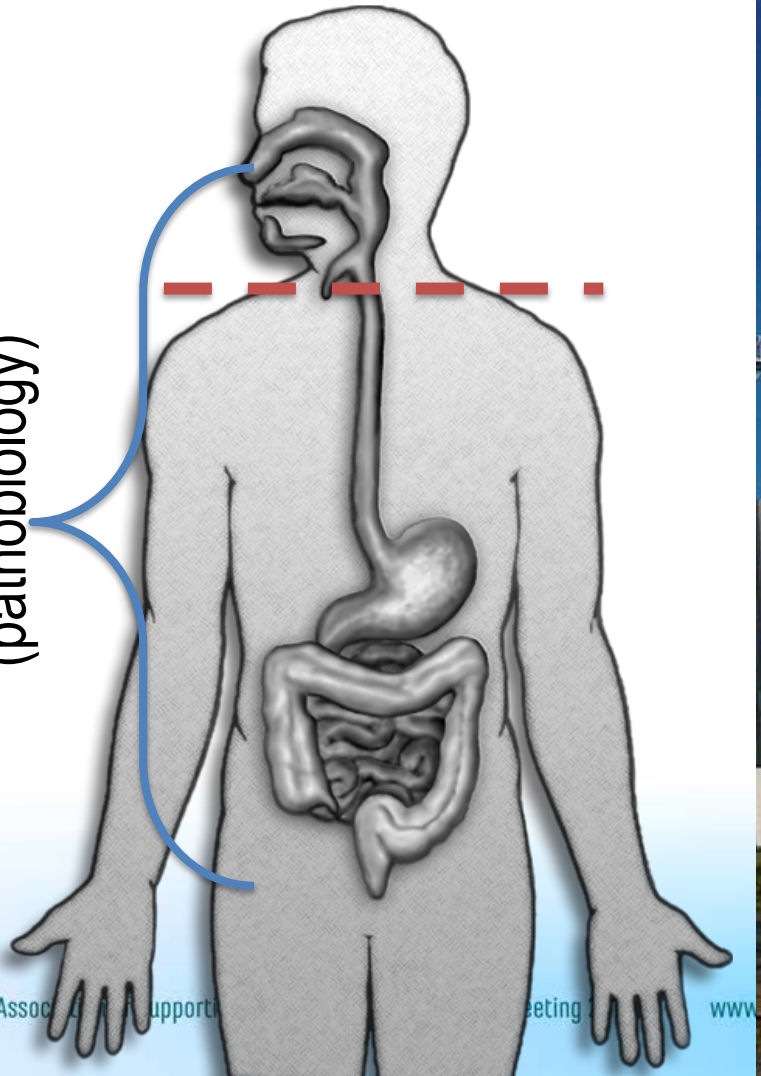
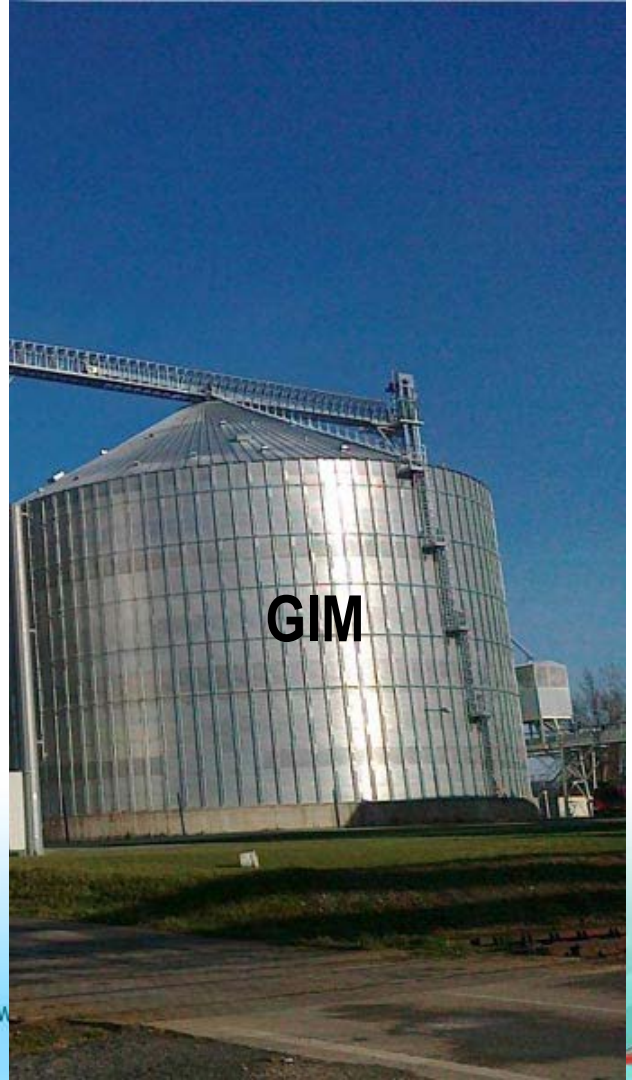
The Multi

Alimentary Tract
(pathobiology)



The Multinational Assoc upport eeting www



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Mucositis – a continuing problem

Treatment	Incidence
Multicycle chemotherapy (solid tumors)	5-40% oral mucositis Up to 50% diarrhea
Conditioning chemotherapy for HSCT	~85% oral mucositis (+TBI) ~40% oral mucositis ~50% diarrhea
Radiotherapy for HNC	60-90% oral mucositis 15-29% diarrhea

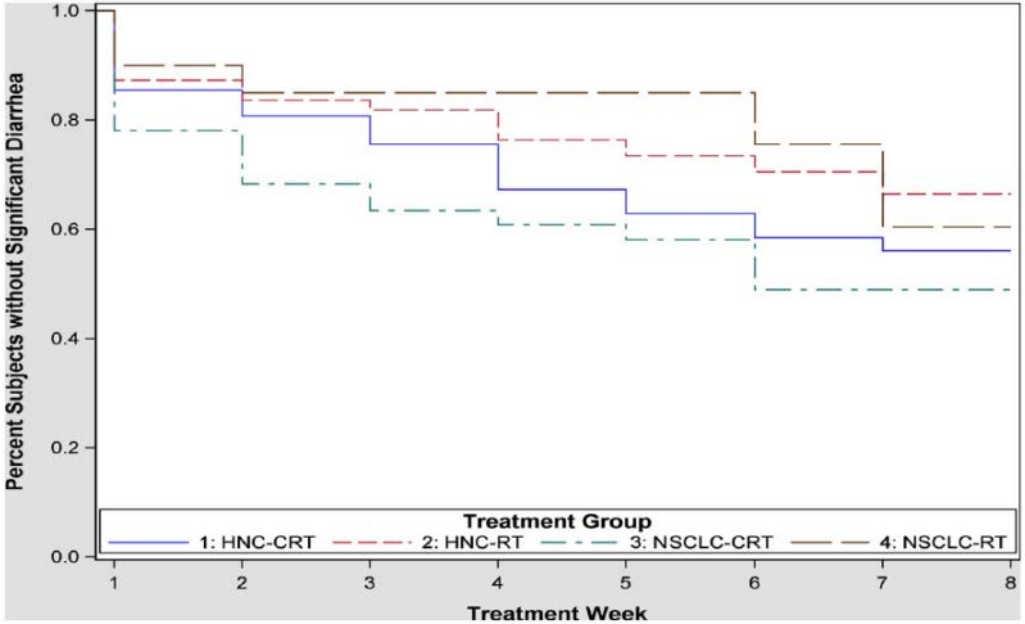
Sonis et al, PharmacoEconomics (2013) 31:753–766

Overlap of pathobiology/symptoms

- Example of local therapy causing GI disturbance

Table 2 Distributin of patients by maximum RID score and treatment groups

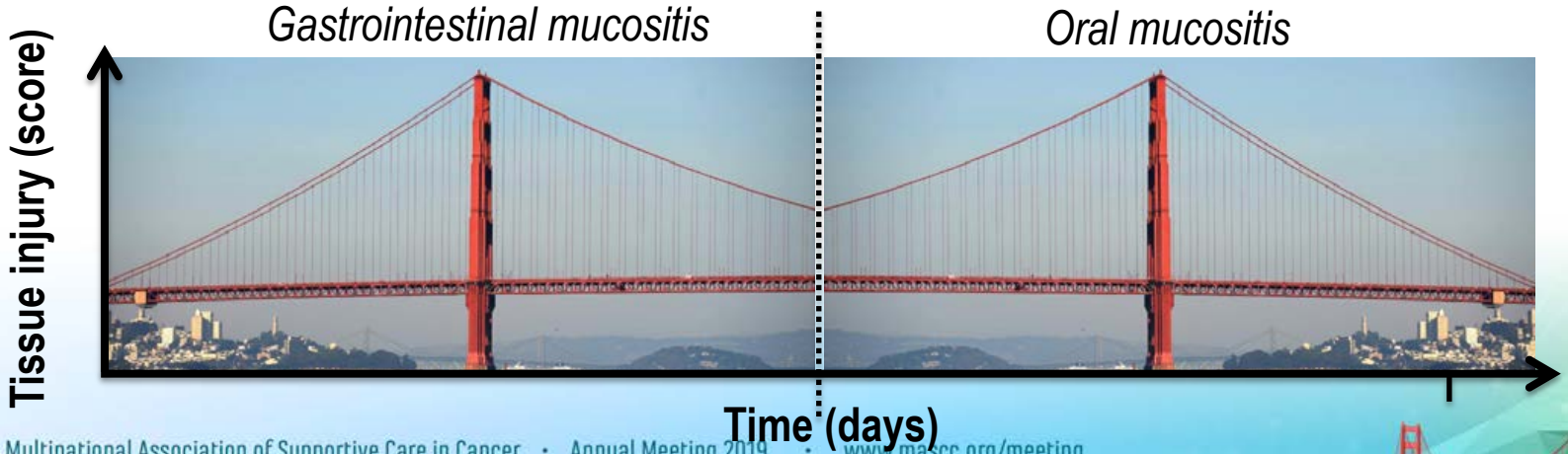
Group	Number of patients	Maximum RID score				
		0 (%)	1 (%)	2 (%)	3 (%)	4 (%)
H and N RT	110	46.4	23.6	16.4	9.1	4.6
H and N CRT	171	33.3	25.7	21.6	14.6	4.7
Lung RT	20	60.0	15.0	15.0	10.0	0.0
Lung CRT	40	26.8	24.4	26.8	17.0	4.9
Total	341	38.3	24.3	20.2	12.9	4.4



Sonis et al, 2015. Supp Care Cancer, 23:433-9

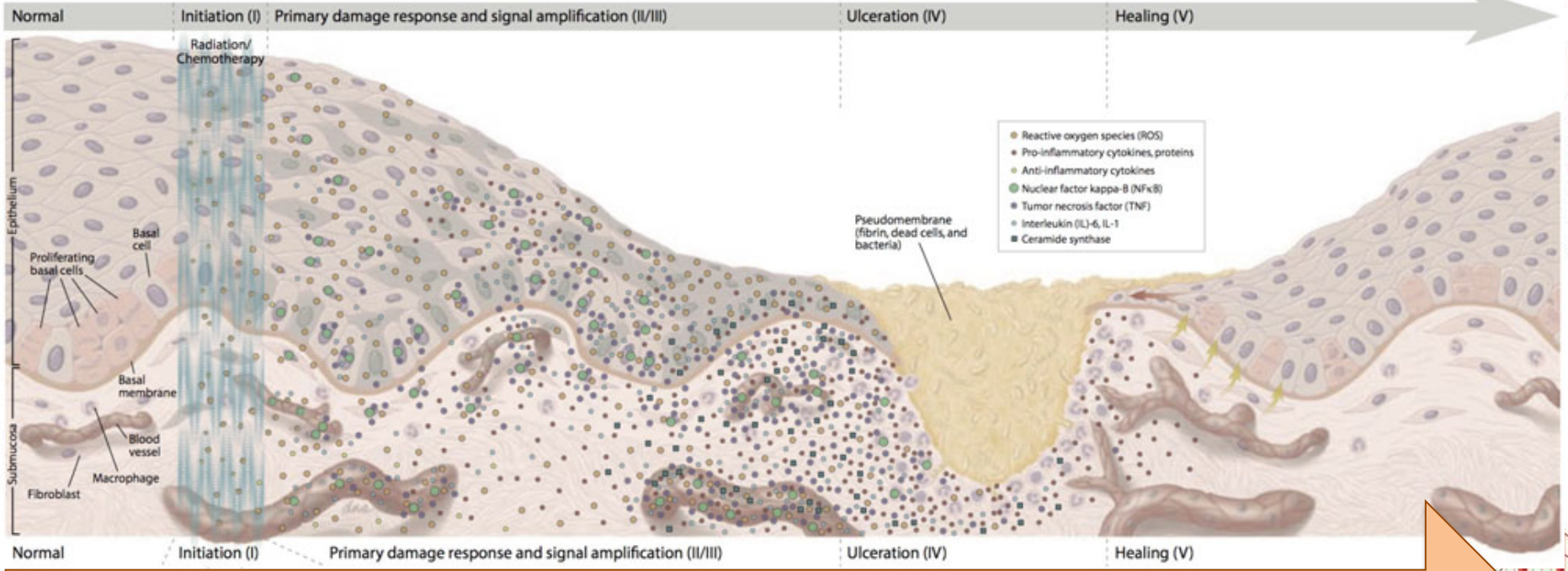
Challenges for OM and GIM research

- Differences in timing dependent on:
  - radiation vs chemotherapy (weeks vs days); regional location (GI ~5 days, Oral ~9 days)
  - Rodents resistance to ulceration



OM Pathobiology

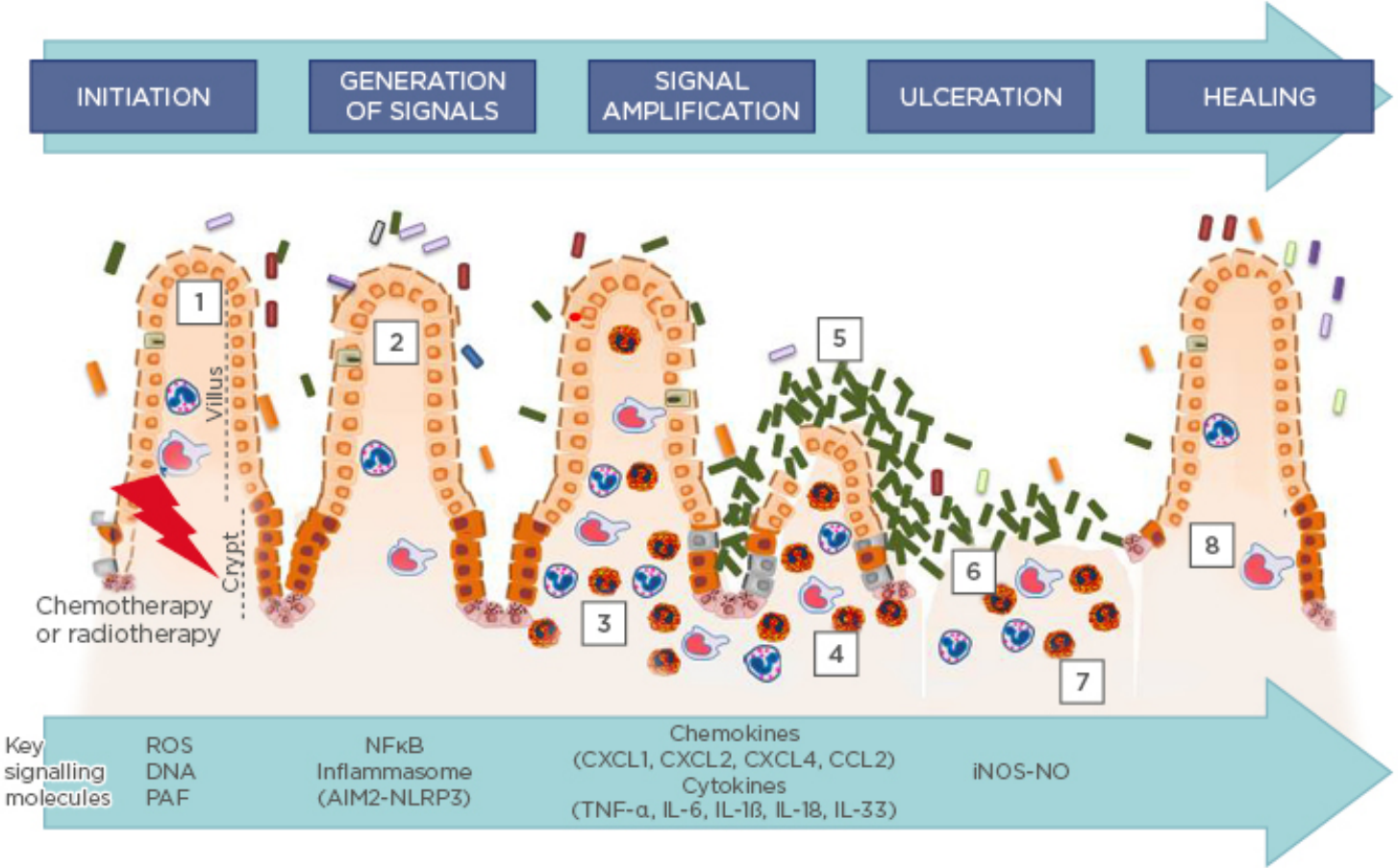
Sonis. J Support Oncol. 2007 5(9 Suppl 4):3-11



Key signalling processes	ROS DAMP release Clonogenic death	NFkB TNF, IL-1b PRR activation	Cell injury & death Innate cell entry TNF, IL-1b, IL-6	Ulcer PAMPs, Innate cells Cytokine feedback	ECM signals Proliferations Migration

GIM Pathobiology

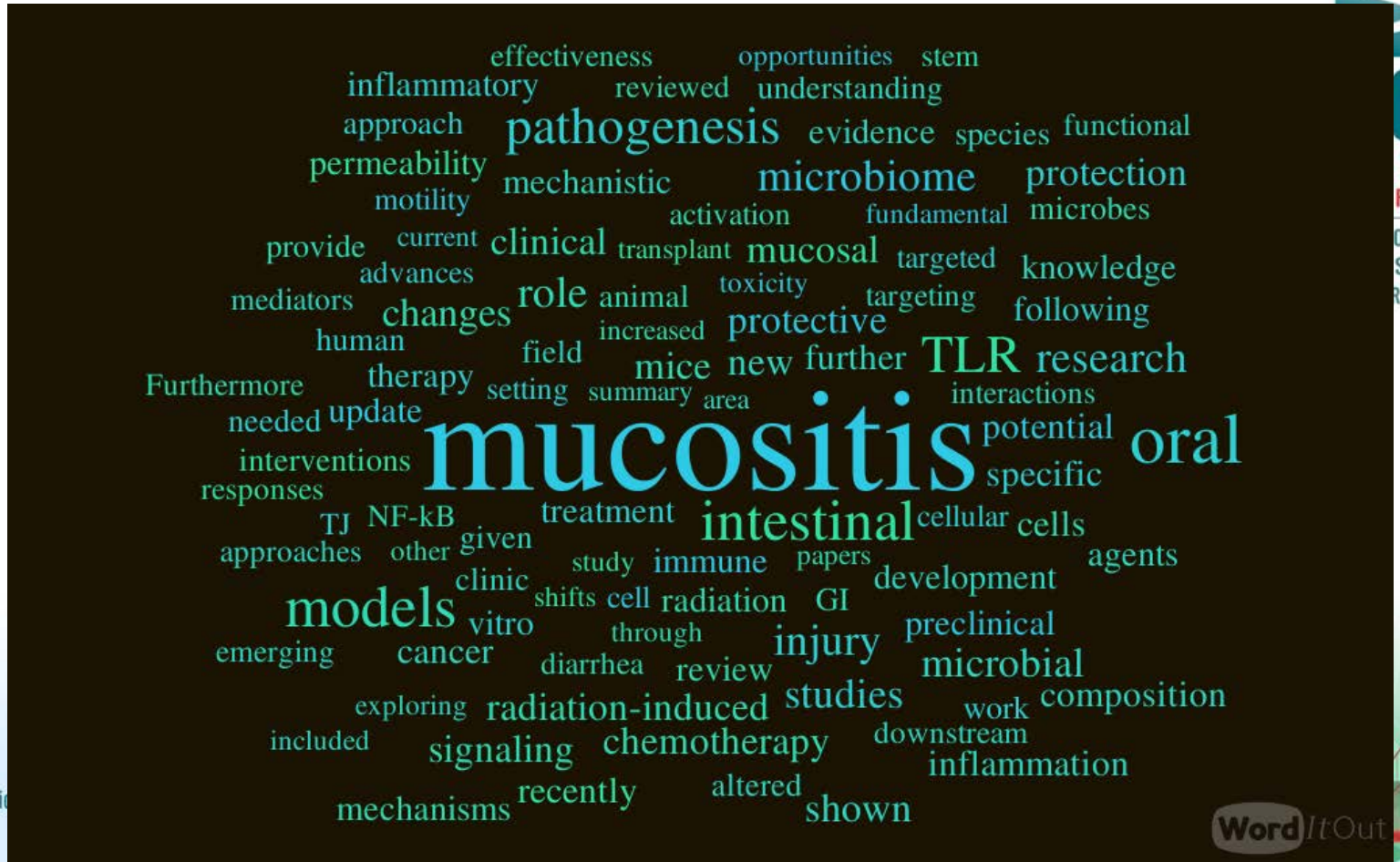
Menezes-Garcia et al, EMJ Gastroenterol. 2018;7:82-91



Pathogenesis review

- Brings both OM and GIM studies (preclinical and translational) together to identify new areas of research, biomarkers, mechanistic targets, experimental interventions.

Pathogenesis review findings



Pathogenesis key areas

- **Established and emerging mediators of toxicity**
  - Microbiome and host immune response
  - Sophisticated targeting of inflammation
  - Altered functional physiology
- **Technological advances**
- **Perspective**

Mediators of toxicity - microbiome

- Shifts in oral microbial composition during development OM has been long recognized and targeted

- Role for gastrointestinal (GI) flora in intestinal injury has only more recently been appreciated but accelerating

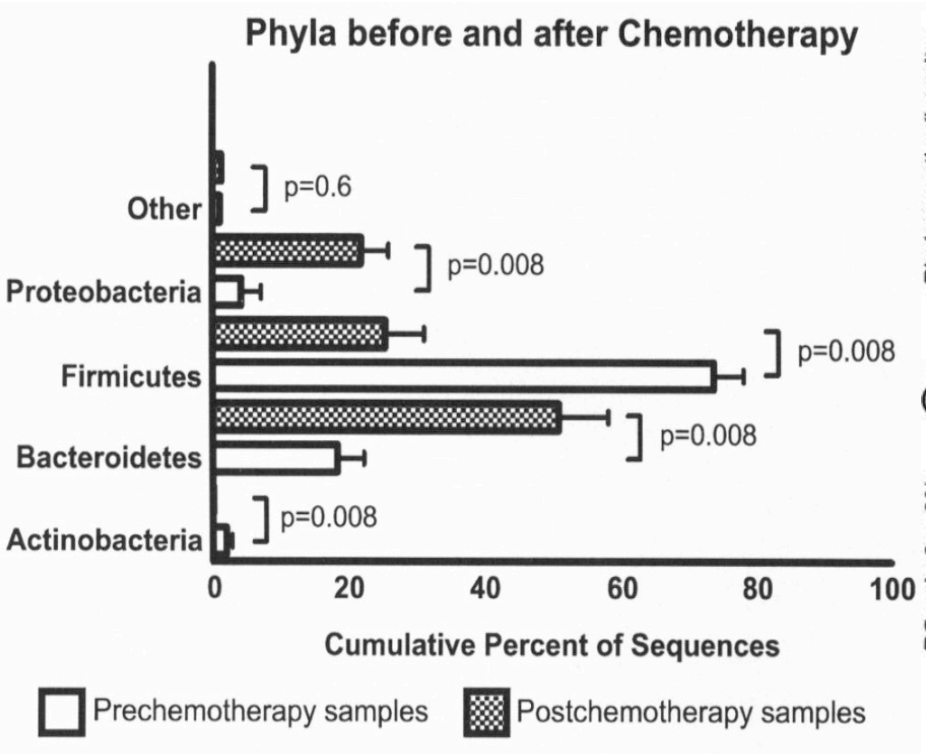
- To be determined is whether baseline composition OR change during therapy is most critical to mucositis development

Mediators of toxicity – oral microbe studies

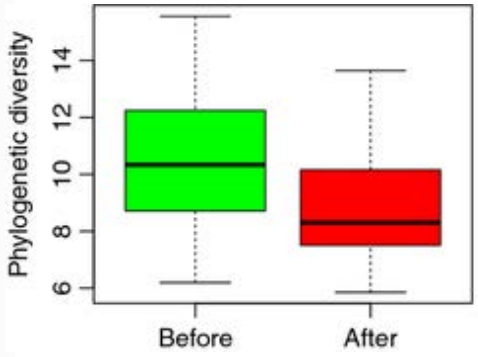
- Patient studies have looked at overall diversity of oral flora and shifts during chemotherapy to determine relationships with oral mucositis risk and severity

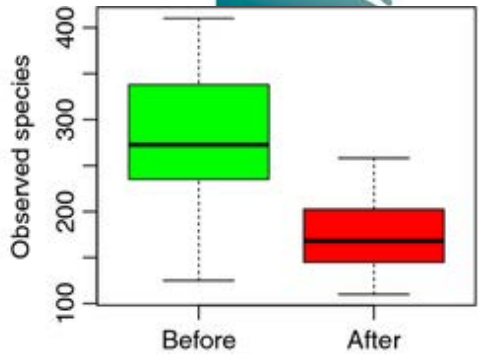
- In vitro models of oral keratinocytes have demonstrated how microbes:
  - impact healing (30% decrease in wound closure)
  - change themselves during exposure to irradiation and 5-FU (sensitivity and virulence)

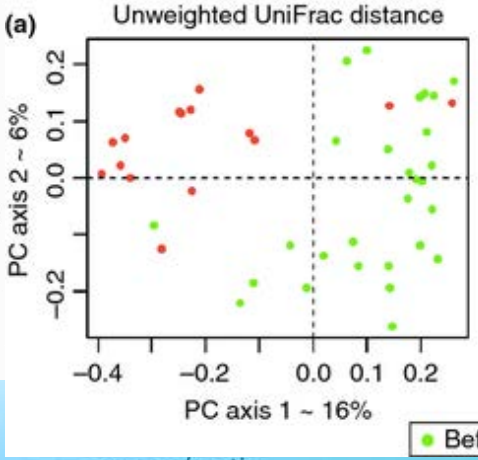
Mediators of toxicity – gut microbe studies

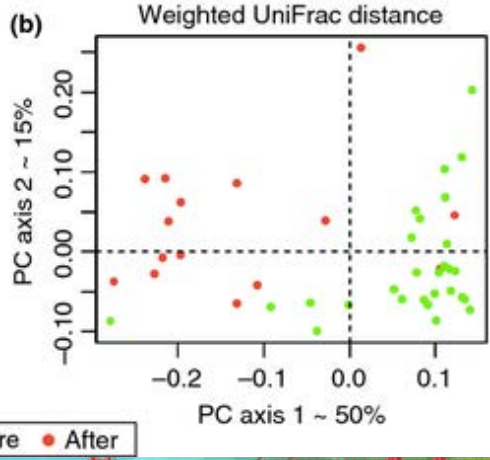


Montassier et al 2014, Microb Ecol 67: 690-9









Montassier et al 2015, AP&T,42: 515-28

Technologies

- **Move from reductionist to systems biology approach**
  - Capitalizing on genomics, proteomics, metabolomics, microbiomics
- **Multi-cellular models (progress but limited complexity)**
  - 3D organoids with microinjection of microbes
  - Gut-on-a-chip with mucus and fluid sheer
  - Mesenchymal stem cells (radiation-induced chronic inflammation models)
- **Germ-free (GF) mice**

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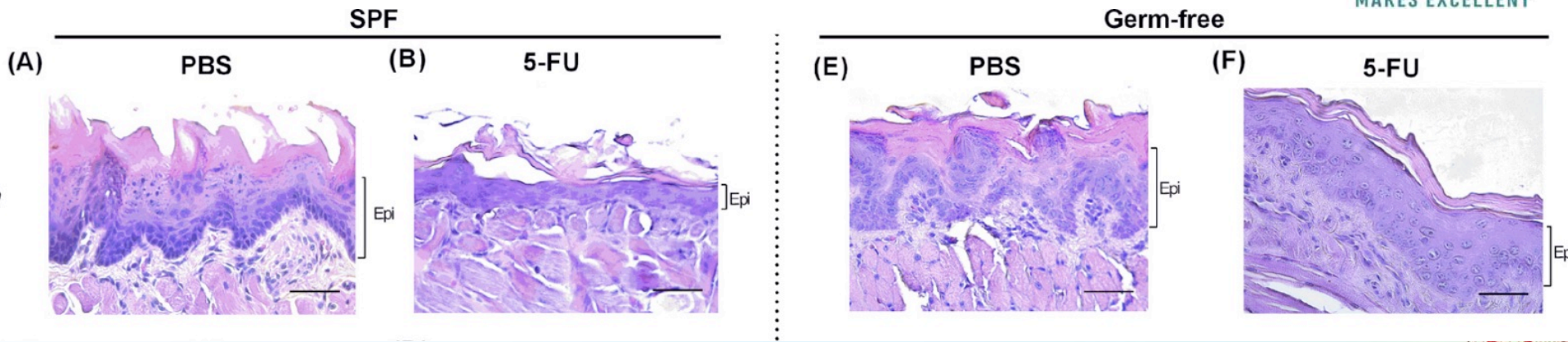
GF mice - OM vs GIM

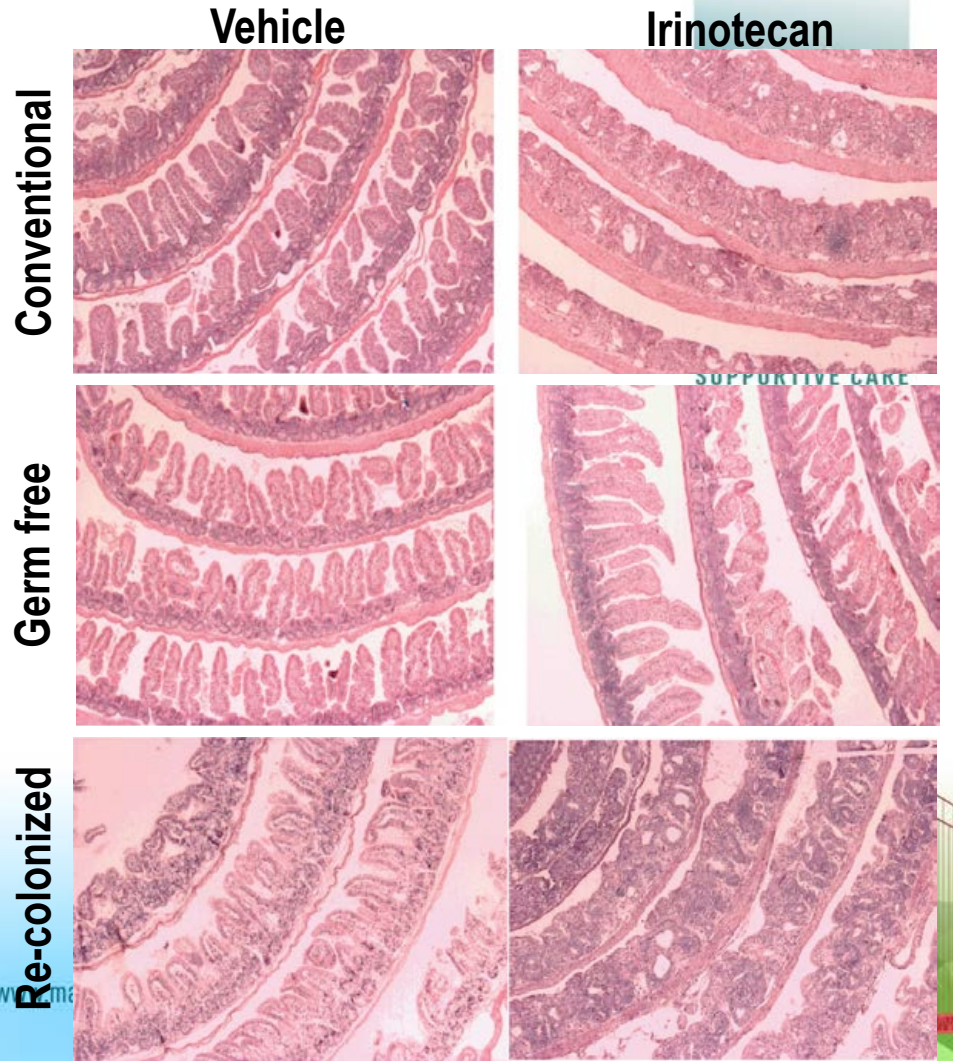
- GF mice are resistant to 5-FU-induced oral mucositis



Gupta et al (2019) , Archives of Oral Biology 101:51–56

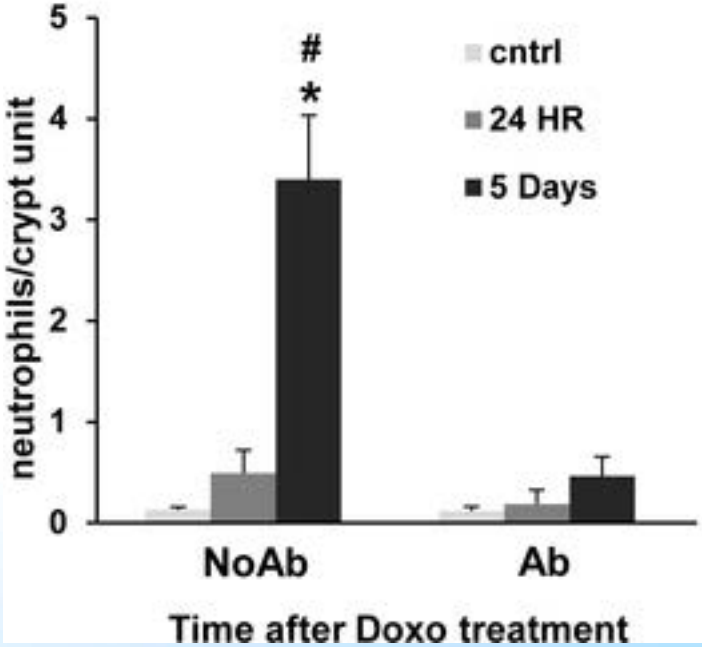
GF mice - OM vs GIM

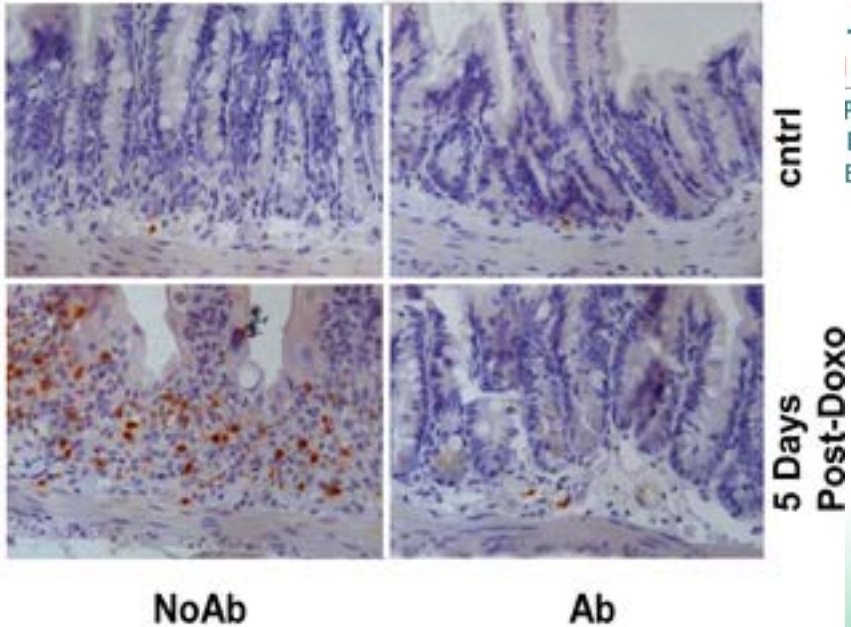
- GF mice are protected from irinotecan GIM
- Conv FMT restores conventional phenotype



Pedroso et al, 2015. Microbiology 161:1950–60

Antibiotics: Chemotherapy-induced





Carr et al, (2017) PLoS ONE 12(3): e0173429

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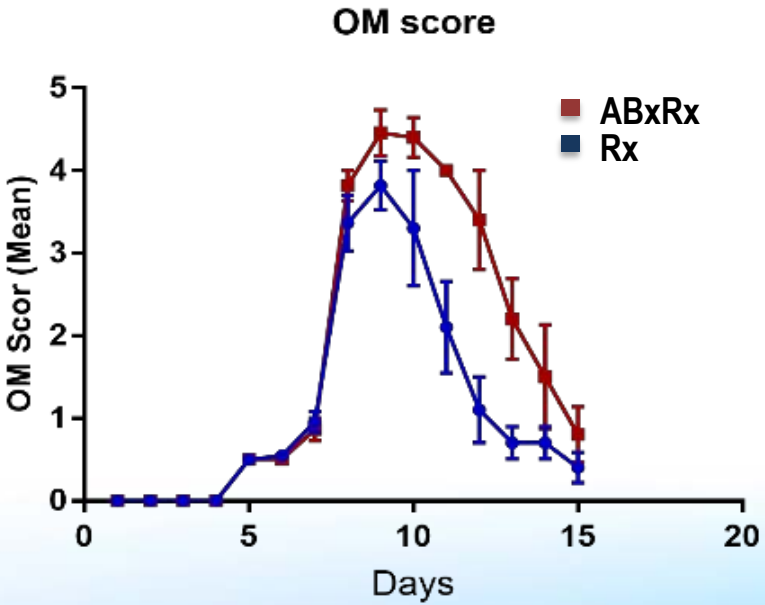
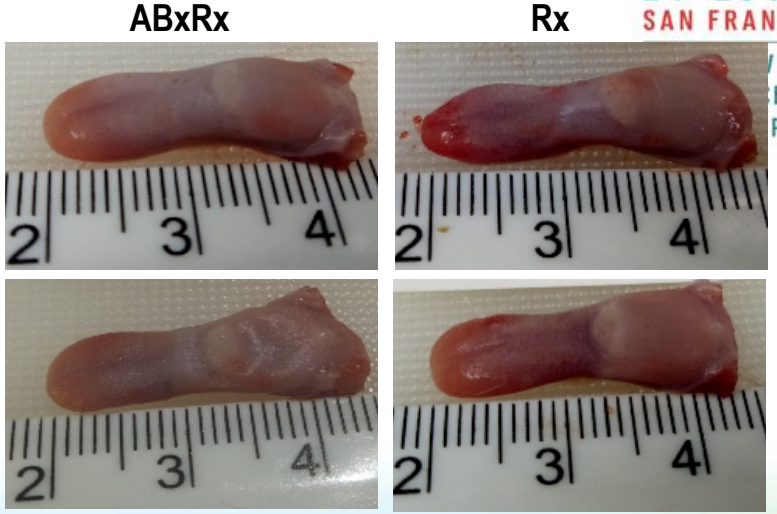
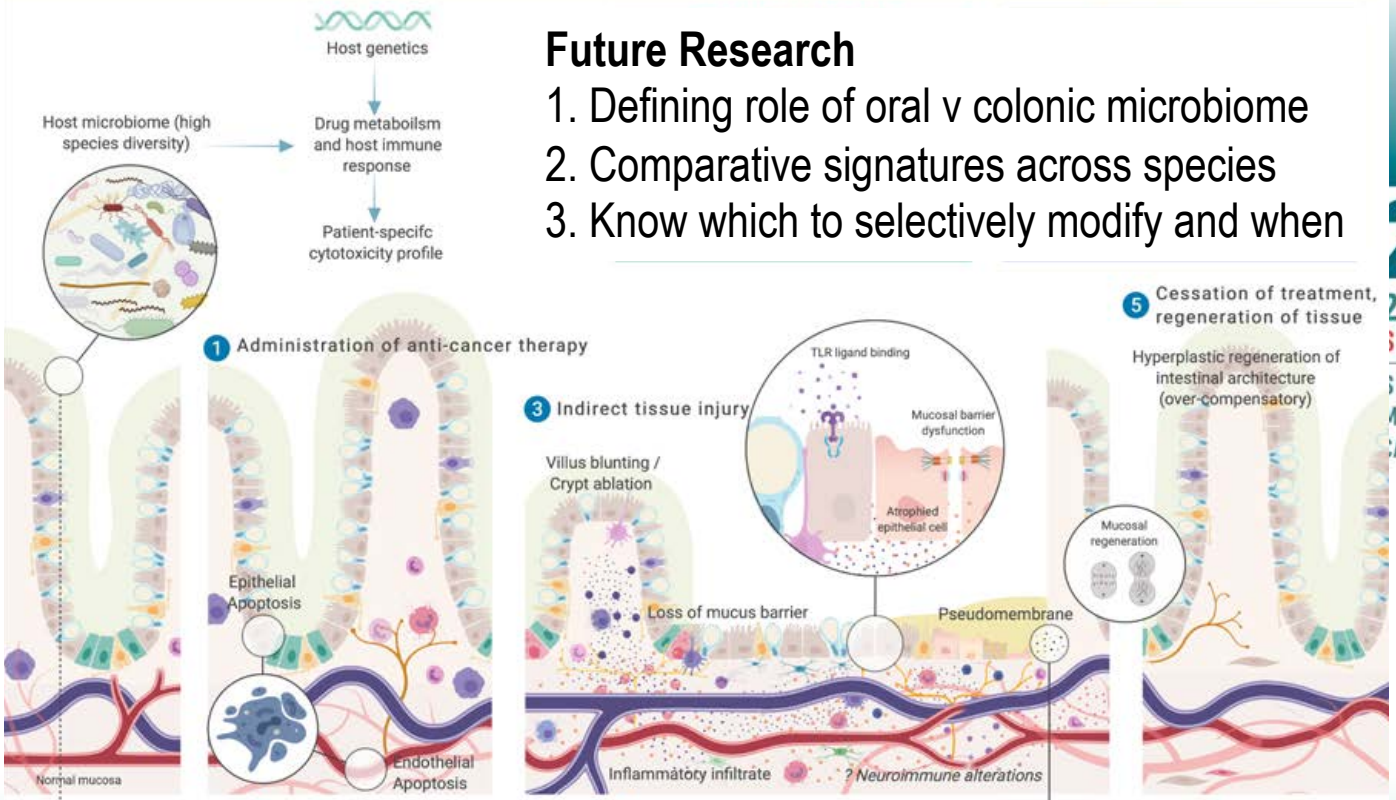
Antibiotics: Radiation-induced OM





Future Research

1. Defining role of oral v colonic microbiome
2. Comparative signatures across species
3. Know which to selectively modify and when



Take home messages

- Microbiome is a new frontier for whole body inflammatory signaling and effort is needed to characterize changes in **different tract compartments**
- Outcome measures in animal models must reflect changes in clinical settings and **whole tract** changes where possible
- Increased complexity of mucositis pathogenesis related to combination regimens - research must get on the leading edge

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