*Integration Between Medical Oncology and Supportive Care: Two Sides of the Same Coin*

# GI toxicity in Oncology: Evolutionary Science

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# Conflict of Interest Declaration

- Helsinn
- GSK
- Merck
- Entera Health

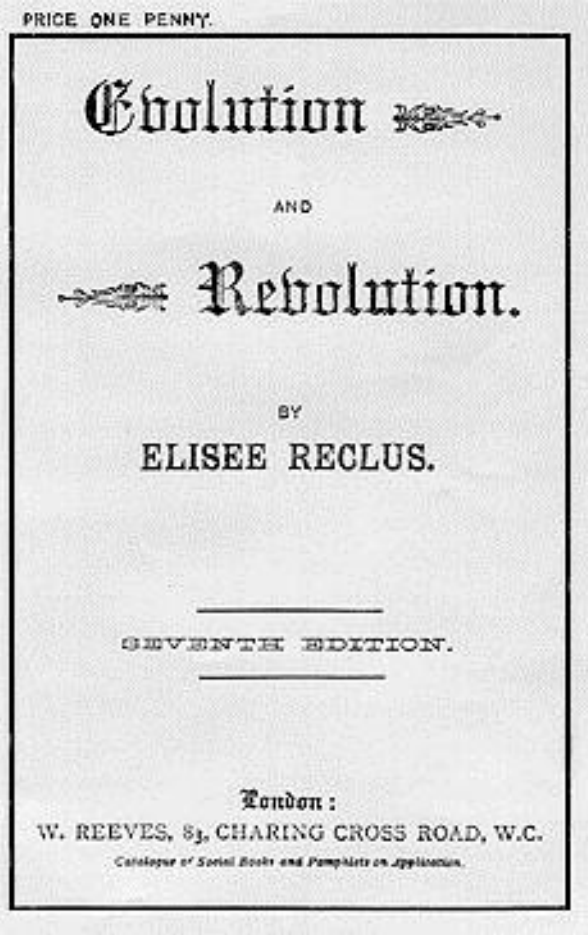
- Consultancies and/or Advisory Boards in area of Supportive Care
- Basic research funding

# Evolution versus Revolution

- Evolution:
  - The gradual development of something, esp. from a simple to a more complex form.
- Revolution:
  - A fundamental change in power or organizational structures that takes place in a relatively short period of time.

- Things get destroyed in both
- Sometimes the speed of revolution is useful.

# 1891: Evolution *versus* Revolution


PRICE ONE PENNY.

Evolution

AND

Revolution.

BY

ELISEE RECLUS.

SEVENTH EDITION.

London:
W. REEVES, 83, CHARING CROSS ROAD, W.C.
Catalogue of Social Books and Pamphlets on Application.

- Closely resemble one another, yet constantly used in social and political sense as though their meaning were absolutely antagonistic.
- Evolution, synonymous with gradual and continuous development in morals and ideas, brought forward as though it were the antithesis of that fearful word, Revolution, which implies changes more or less sudden in their action, and entailing some sort of catastrophe.

*Elisee Recluse; Anarchy Archives*

# Short History of Supportive Care

- 400 BC: Hippocrates
  - Don’t treat cancer as treatment shortens life
- 1800 AD: Ehrlich
  - Need for magic bullet to kill cancer & spare normal tissue
- 1900s: Curies
  - Die of cancer while curing cancer with Radium
- 1950: Faber
  - Cancer requires total care

# Short History continued

- 1950s: Frei and Freireich
  - Successful leukemia treatment extremely toxic (NCI Butcher shop reference)
- Aggressive combination therapy accompanied by very significant side effects
- Oncologists too often concerned with cure than care
  - afraid that even pain relief would be detrimental
- Oncology nursing became more important
- Gastrointestinal toxicities could be life-threatening

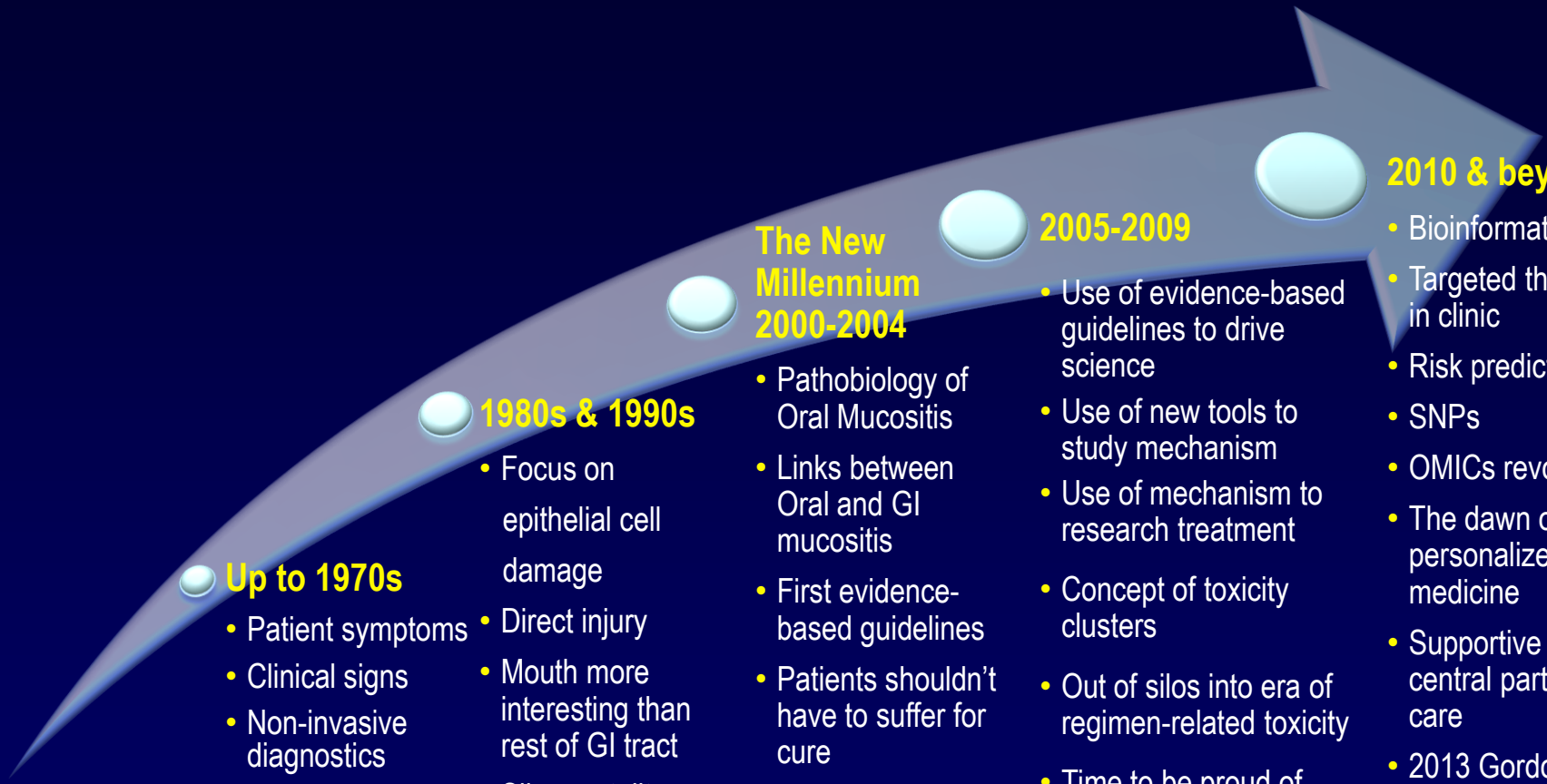
# Supportive Care in Cancer

- 1987: first meeting in Switzerland, evolved into MASCC by 1991
- Management of symptoms of cancer and its treatments:
  - Physical
  - Psychological
  - Rehabilitation and Survivorship
- Anti-tumour effect must not be compromised
- Personalised Cancer Medicine involves both tumour and toxicity

# Holding out for a miracle

- **RICHARD GUILLIATT** in: The Australian September 22, 2012
- Gerson regimen
  - 10 raw juices & 5 coffee enemas a day,
  - mineral supplements
  - strict vegan diet.
- $15,000 on 3-week stay at Gerson clinic in Mexico
- Website-The Wellness Warrior
  - posts advice and updates on her condition
  - feels the body, mind and spirit is what needs to be healed
  - theme
    - that natural remedies are superior to toxic and traumatising effects of chemotherapy and radiation
    - that healing is in large part a matter of belief.
    - as long as I do everything to bring my body back into balance, as long as I take responsibility for my healing, no reason I couldn't heal."

# Gastrointestinal Toxicity Evolution



**Up to 1970s**

- Patient symptoms
- Clinical signs
- Non-invasive diagnostics
- Histopathology and IHC
- Patients have to suffer for cure

**1980s & 1990s**

- Focus on epithelial cell damage
- Direct injury
- Mouth more interesting than rest of GI tract
- Silo mentality

**The New Millennium 2000-2004**

- Pathobiology of Oral Mucositis
- Links between Oral and GI mucositis
- First evidence-based guidelines
- Patients shouldn't have to suffer for cure

**2005-2009**

- Use of evidence-based guidelines to drive science
- Use of new tools to study mechanism
- Use of mechanism to research treatment
- Concept of toxicity clusters
- Out of silos into era of regimen-related toxicity
- Time to be proud of supportive care research

**2010 & beyond**

- Bioinformatics
- Targeted therapy in clinic
- Risk prediction
- SNPs
- OMICs revolution
- The dawn of real personalized cancer medicine
- Supportive care is central part of cancer care
- 2013 Gordon Research Conference

# Changing Epidemiology

Cancer treatments change constantly

- Every new class of drugs brings new toxicity
- Increased sophistication reveals hitherto hidden toxicity
  - Normal tissue radio-sensitivity
  - Bystander effects

Implications for

- Toxicity profile
- Pathobiology of toxicity
- Treatment/prevention of toxicity

# Risk Prediction

- Traditionally not very good
- Patient factors
  - Age
  - Sex
  - Alcohol intake
  - Diabetes
  - Weight
  - Past Cancer History
- Drug factors
  - Which drug
  - Frequency, dose, route
  - Combinations
- Tumour factors
  - Solid *versus* Haematological
  - Extent of disease

# Inter-patient variability

- Why some patients develop toxicity and others do not is an ongoing puzzle
- Why is it that two people with simliar
  - demographics,
  - tumours
  - and treatment regimens

have such disparate experiences with toxicity?

# Inter-patient variability

- Virtually every important biological pathway is genetically controlled
  - differences in gene expression are key risk determinants.
- Oxidative stress & pro-inflammatory cytokines implicated in GI toxicity
  - Sharp increases in ROS almost immediately after drug or radiation trigger cascade of events leading to tissue destruction
  - studies have identified deletion SNPs associated with increased risk of GI toxicity

# Predicting Toxicity: The Old Paradigm

- Assumes there is a single "master gene" or individual SNPs that are associated with risk
- Focused on:
  - Drug metabolism
  - Direct cell response to drug
  - Bystander biologic targets of drug

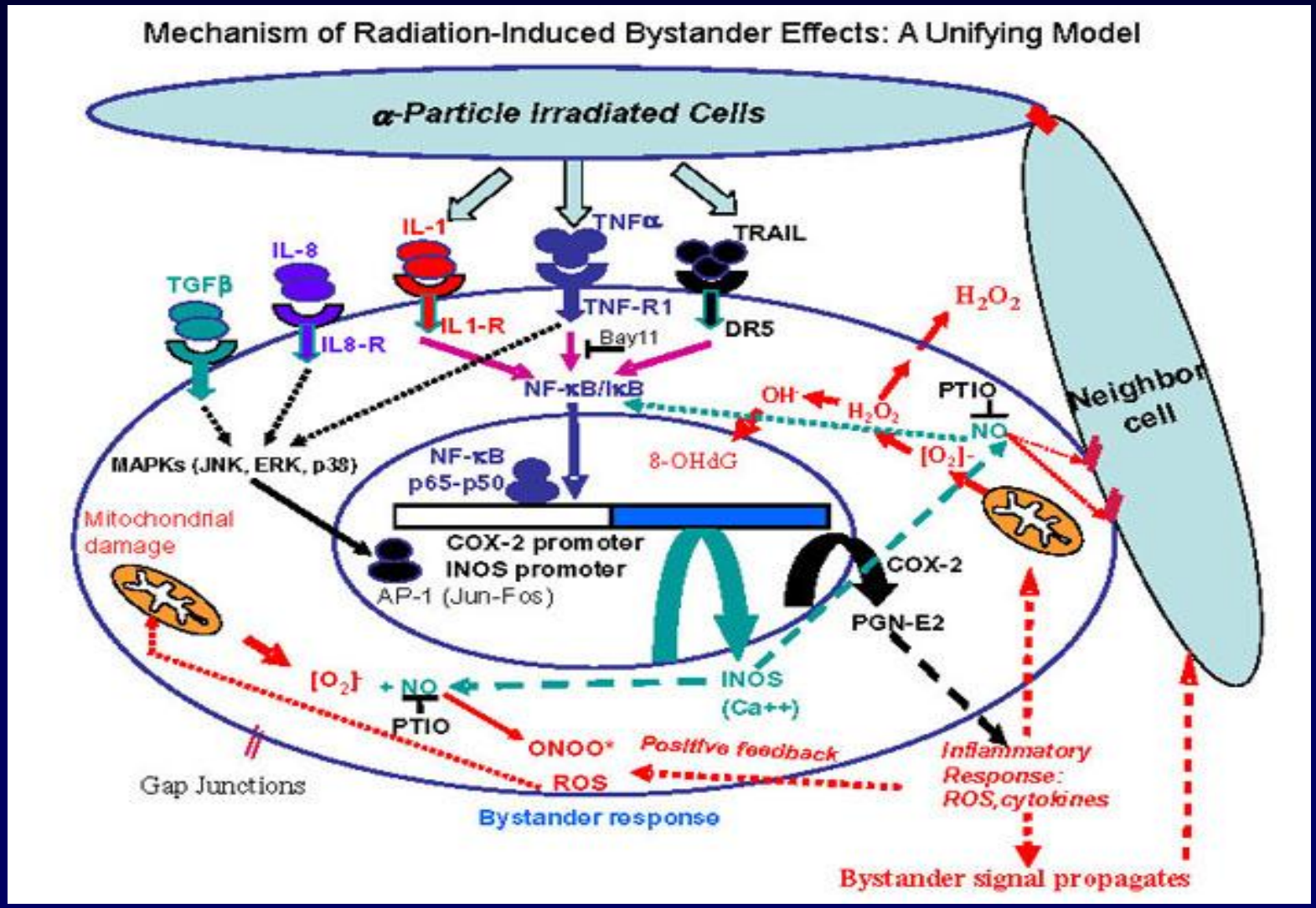
# Risk prediction future

- Comprehensive assessment of genetically based risk.
- Phenotype more likely due to team of genes than single master gene
- Bayesian networks derived from unsupervised and learned networks of genes or SNPs
  - Not hypothesis driven
  - No threshold expression values required
  - Algorithms test and re-evaluate predictive value to arrive at cluster of greatest predictive power
  - Defined cluster then validated prospectively

# Bystander Effects

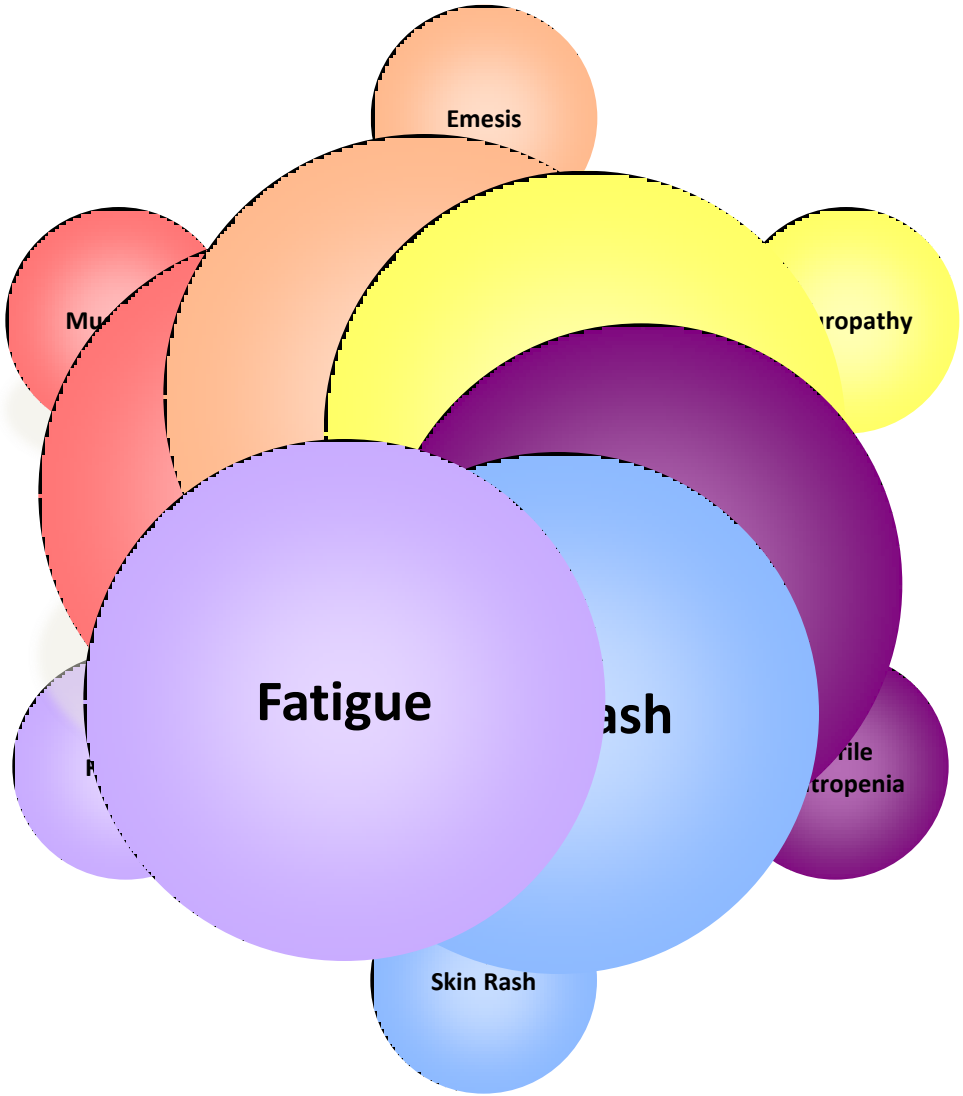
- Long considered that RT damage is due to DNA damage in irradiated cells (un- or mis-repaired)
- Now know that non-targeted cells also damaged = bystander response
  - Proposed mechanisms include
    - Secreted soluble factors
    - Oxidative metabolism
    - Gap-junction intercellular communication
    - DNA repair

# The Bystander Effect

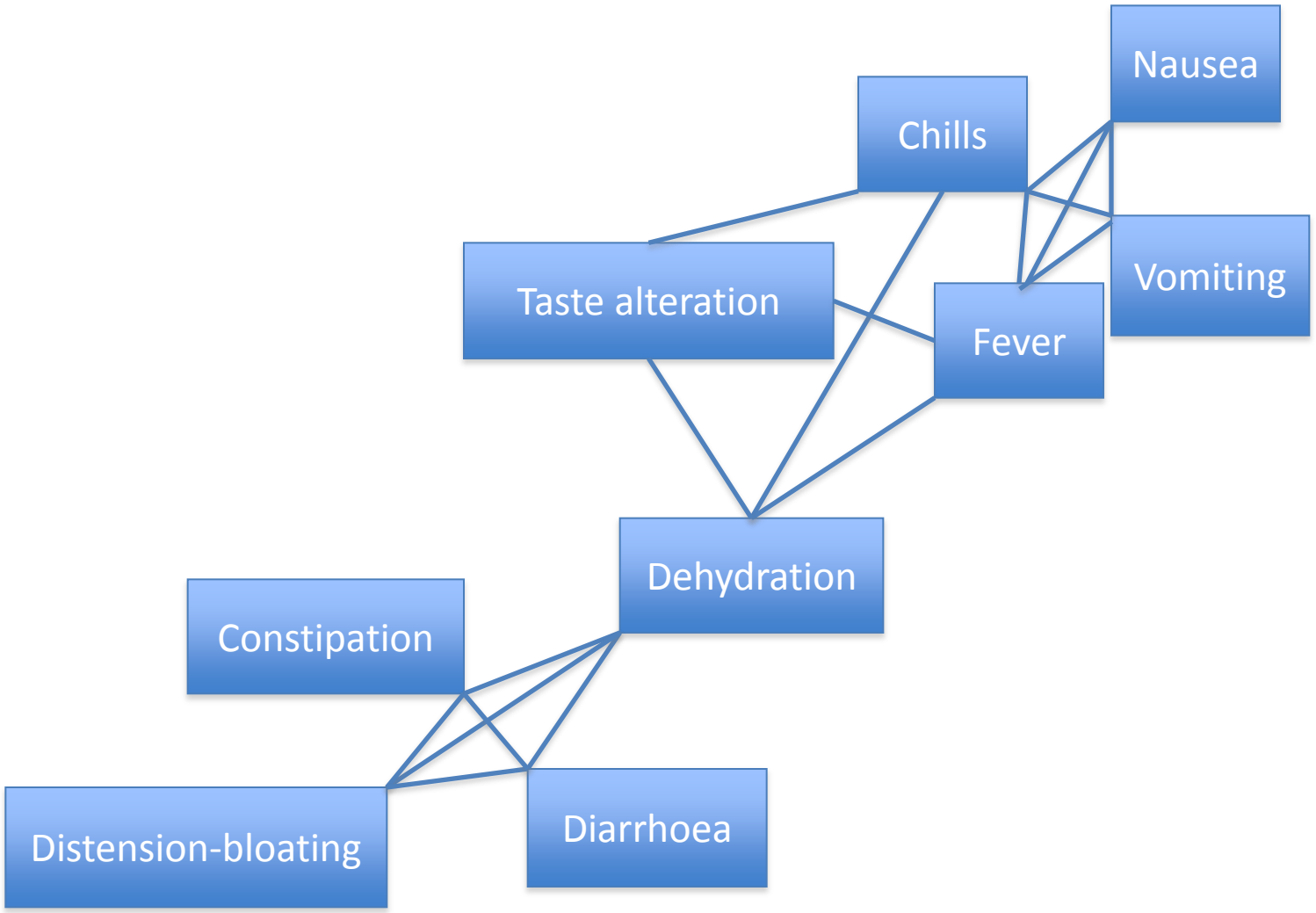



S. Sonis

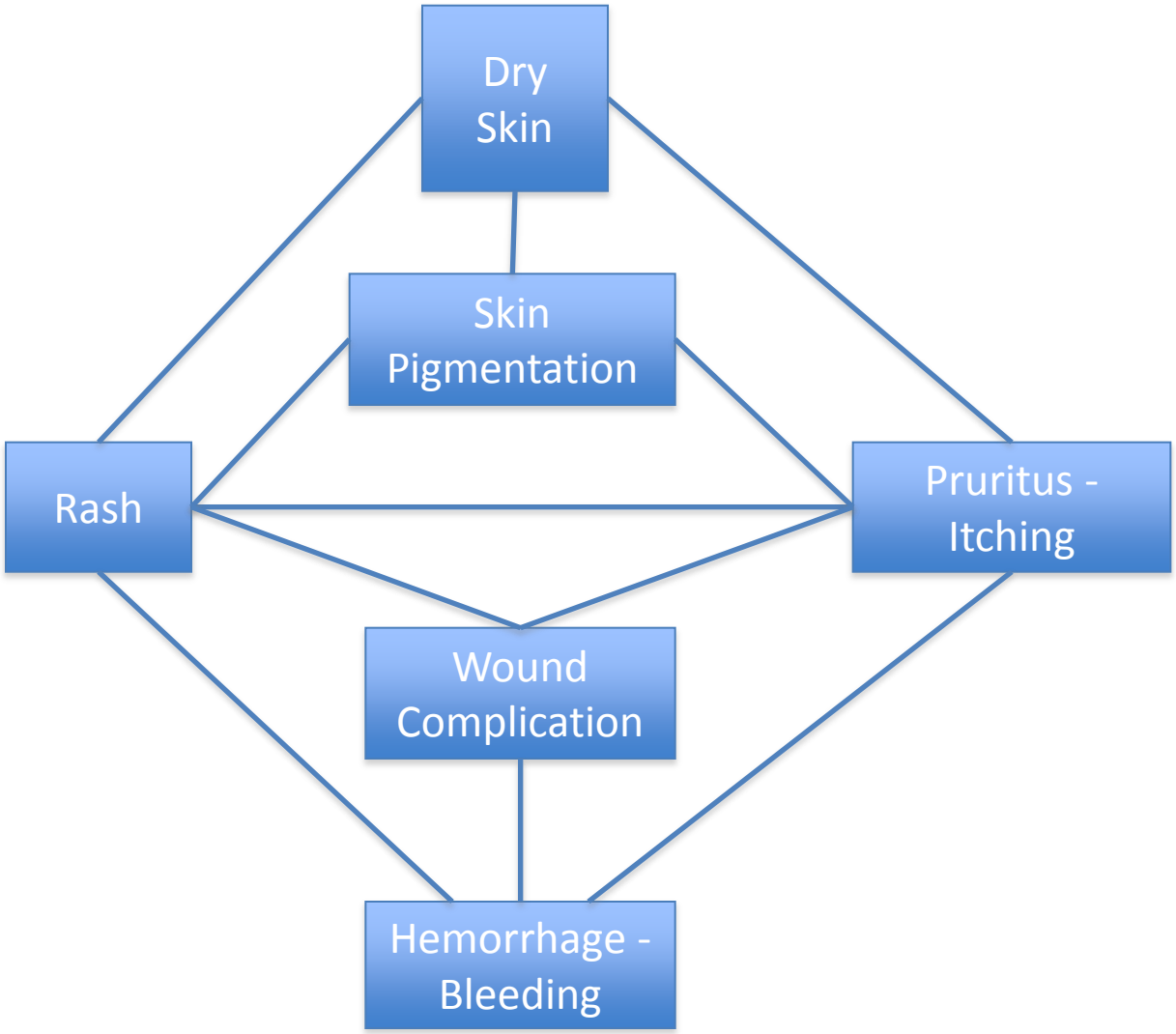
# Compartmentalization



# Gastrointestinal Symptom Cluster



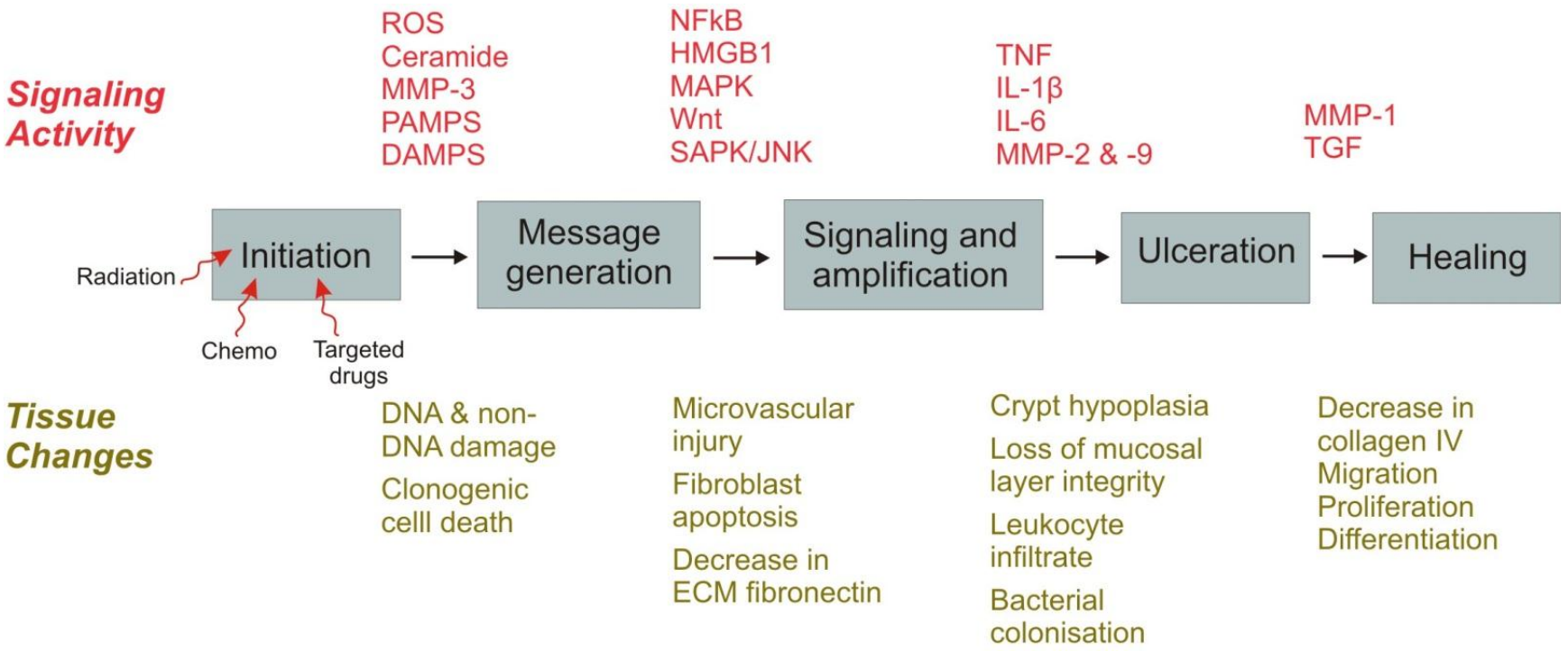
# Dermatological Symptom Cluster



# What does this mean?

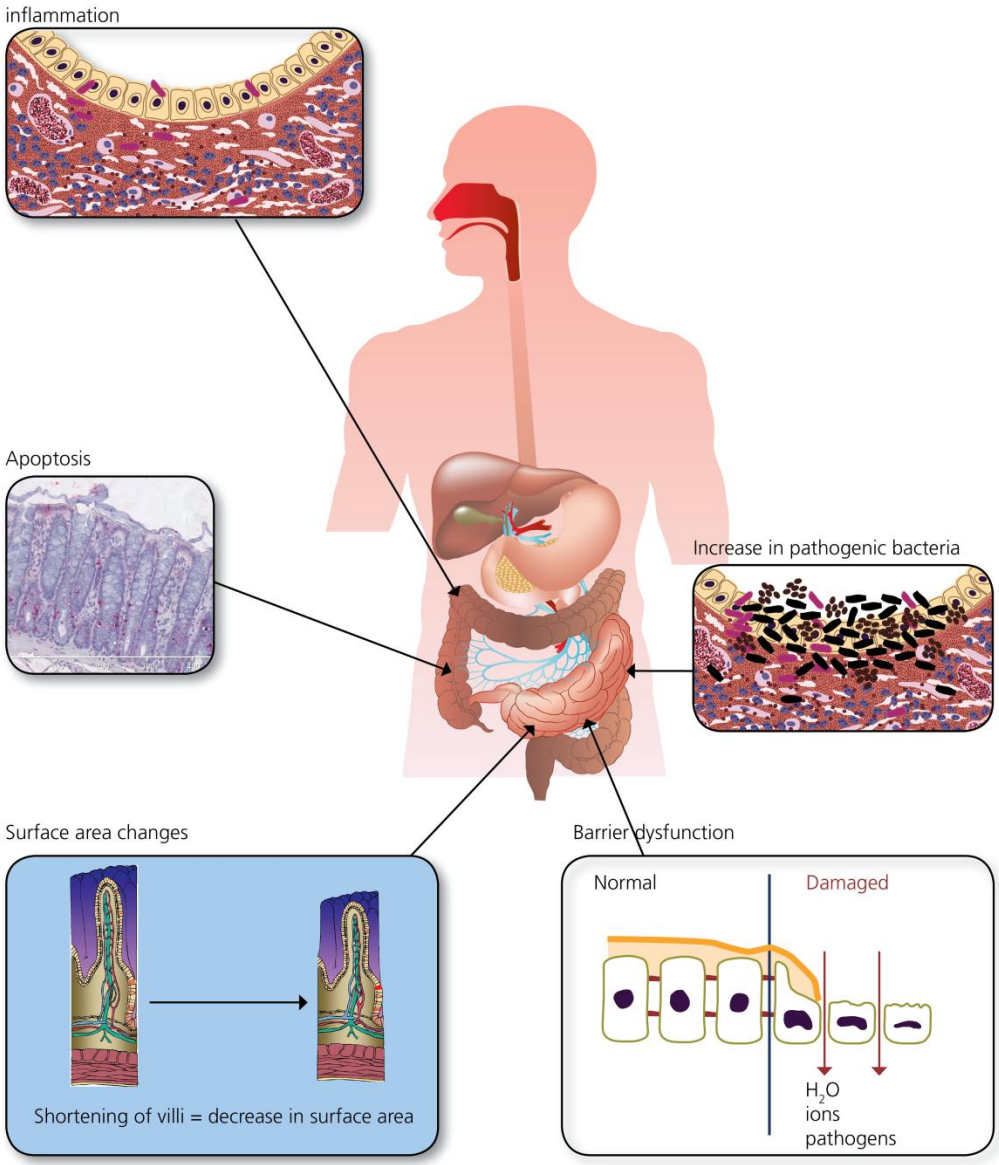
- Toxicities linked in a cluster may have a common pathobiology
- This may lead to a common treatment
  - Reduction of multiple toxicities with a single intervention
- More work is needed to show if this holds for all cancers and all treatments

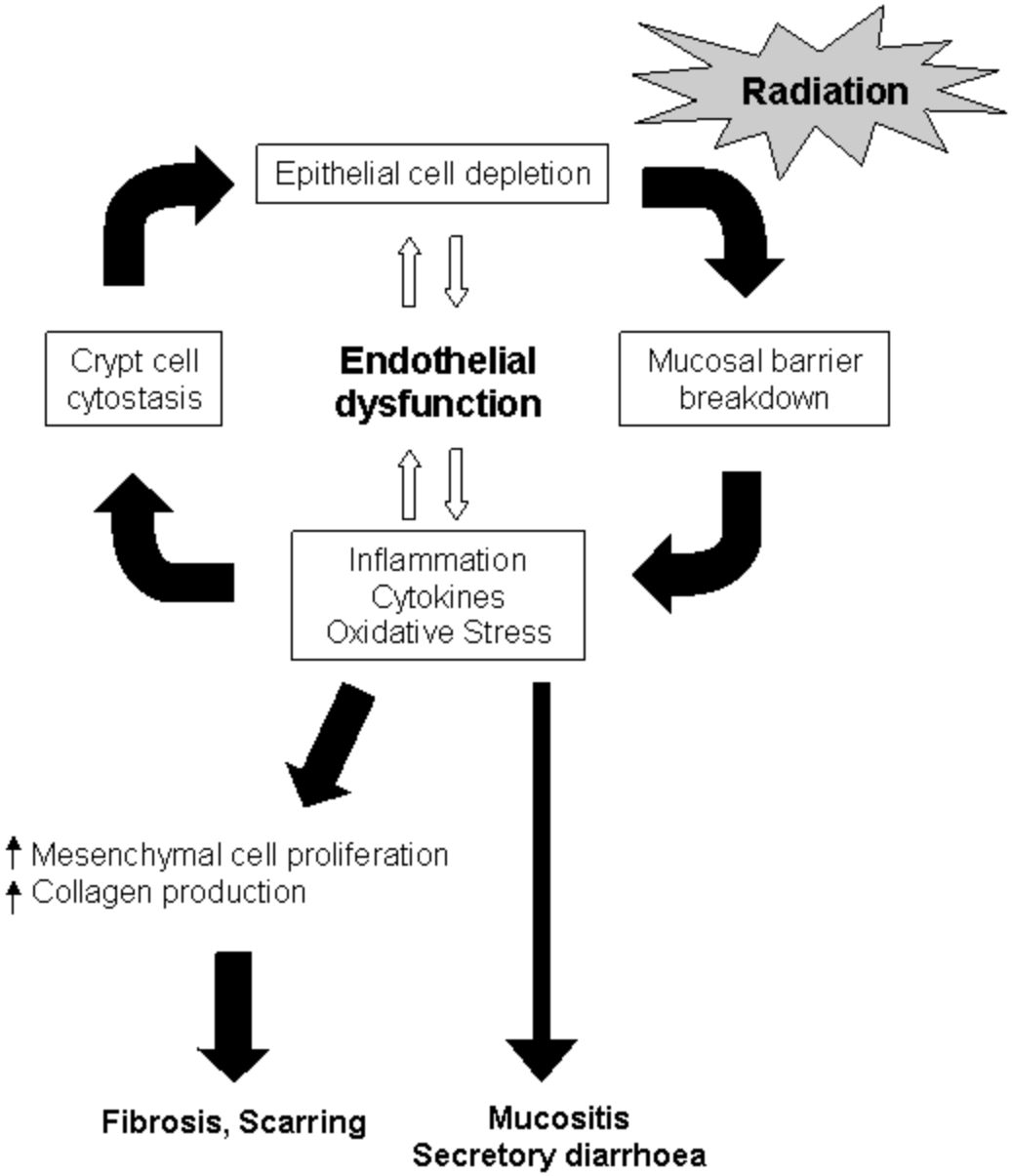
# Mechanism of Mucositis




*Al-Dasooqi 2012*

# The histo-pathological features of GI toxicity






The interactions between tissue factors affected by radiation in the intestine which leads to acute intestinal radiation toxicity and subsequently sustains the chronicity of radiation-induced fibrosis.

# What is causing the damage?

- Interaction between
  - Patient
  - Tumour
  - Drug/Radiation
- Interaction between
  - Gut wall
  - Gut contents
    - Gut Flora
    - Oral intake
    - Gut secretions/mucus

# Examples of Interventions Tested in Animal Models

| Intervention | Model species |
|---|---|
| KGF (palifermin) | Mouse, Rat, Hamster |
| FGF-20 (velafermin) | Mouse, Rat, Hamster |
| IL-11 | Mouse, Rat, Hamster |
| EGF | Mouse, Hamster |
| TGF-β | Mouse, Rat, Hamster |
| TGF-α | Rat |
| WDGFE | Rat |
| Probiotics | Rat |
| Sodium selenite | Mouse |
| Amifostine | Mouse, Rat |
| IB-367 | Hamster |
| SCV-07 | Hamster |
| ITF | Mouse |
| Glutamine | Mouse, Rat |

# Treatment of mucositis

- MASCC mucositis guidelines (www.mascc.org)
- Patient responsibility for own mouth care
- Good Oral Hygiene
- Any basic mouthwash
- Palifermin in transplant
- Ice chips for short plasma half-life drugs
- (Gelclair, glutamine etc)

# Treatment of GI Mucositis

- Omeprazole or ranitidine for epigastric symptoms
- Loperamide for diarrhoea
- Octreotide if loperamide fails
- Reduce
  - lactose-containing products
  - Spicy foods
- Antibiotics if develop GI syndrome
- (Diurnal variation in RT side effects)

# Mechanisms of CT-Induced Nausea & Vomiting

- **Central**
  - Dorsal vagal complex
  - Area postrema

Brainstem
**NK-1** receptors
Substance P

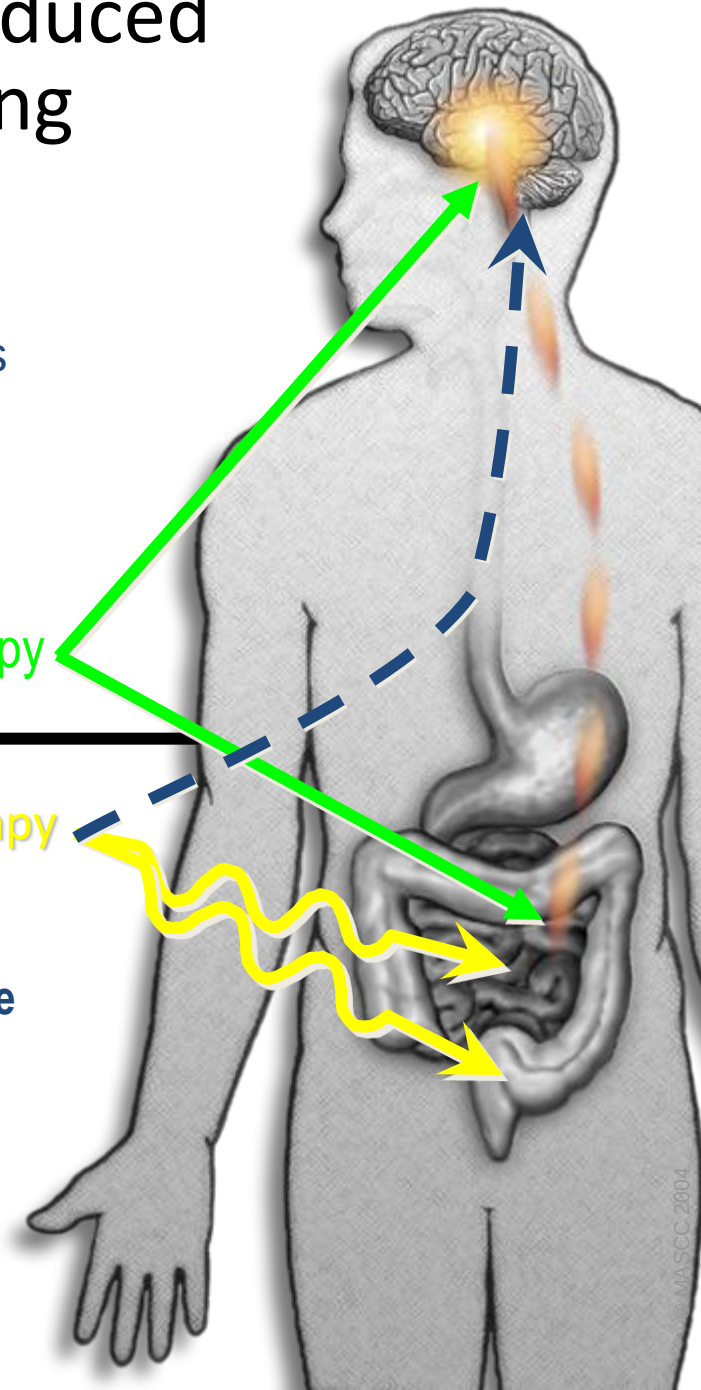
Chemotherapy

Radiation Therapy

**Peripheral (GI)**

- 5-HT receptors on enterochromaffin cells of the GI tract & NK-1 receptors on bowel smooth muscle

**Serotonin release**
**Vagal afferents**
**5-$HT_3$ receptors**
**NK-1 receptors**



©MASCC 2004

# Small molecules

- Inhibitors of signal transduction
- Normal cells have these signalling pathways
- Similar to effects of monoclonal antibodies but down-stream
- Similar effects lead to similar toxicities
- Diarrhoea is a DLT for most small molecule inhibitors of EGFR tyrosine kinase
- Mechanism of diarrhoea not reported

# TKI diarrhoea model

- Wistar rats
- Lapatinib as demonstration TKI
  - Dose finding
  - Morphology
  - Concentration versus effect
- Combination with taxanes

- Daily lapatinib at doses > 100 mg/kg induces diarrhoea
- Similar pattern to human
- Mild histopathological changes compared with CT or RT
- Diarrhoea severity related to local gut changes, not serum concentration
  - may impede drug absorption.
- Suggests lapatinib-induced diarrhoea is secretory, due to electrolyte imbalances secondary to epithelial changes.

**Oral lesions associated with inhibitors of mammalian target of rapamycin in cancer patients**

Ulcerative mucositis from, cytotoxic chemotherapy: extensive, deep ulceration of the ventral tongue. The pseud-omembrane covering the ulcer is thicker than with mTOR inhibitor assoicated stomatitis (mIAS) ulcers. Typically, the architecture of mucositis-associated ulcers is not defined as well as ulcers associated with mIAS.

Minor (L) and Major (R) aphthous stomatitis from mTOR inhibitors. Note the shallow ulceration and peripheral erythema, and the irregular edge of the major ulcers. These are extremely painful.

**Cancer**
Volume 116, Issue 1, pages 210-215, 27 OCT 2009 DOI: 10.1002/cncr.24696

# Treatment of mTOR Inhibitor-Associated Stomatitis

Standard treatment

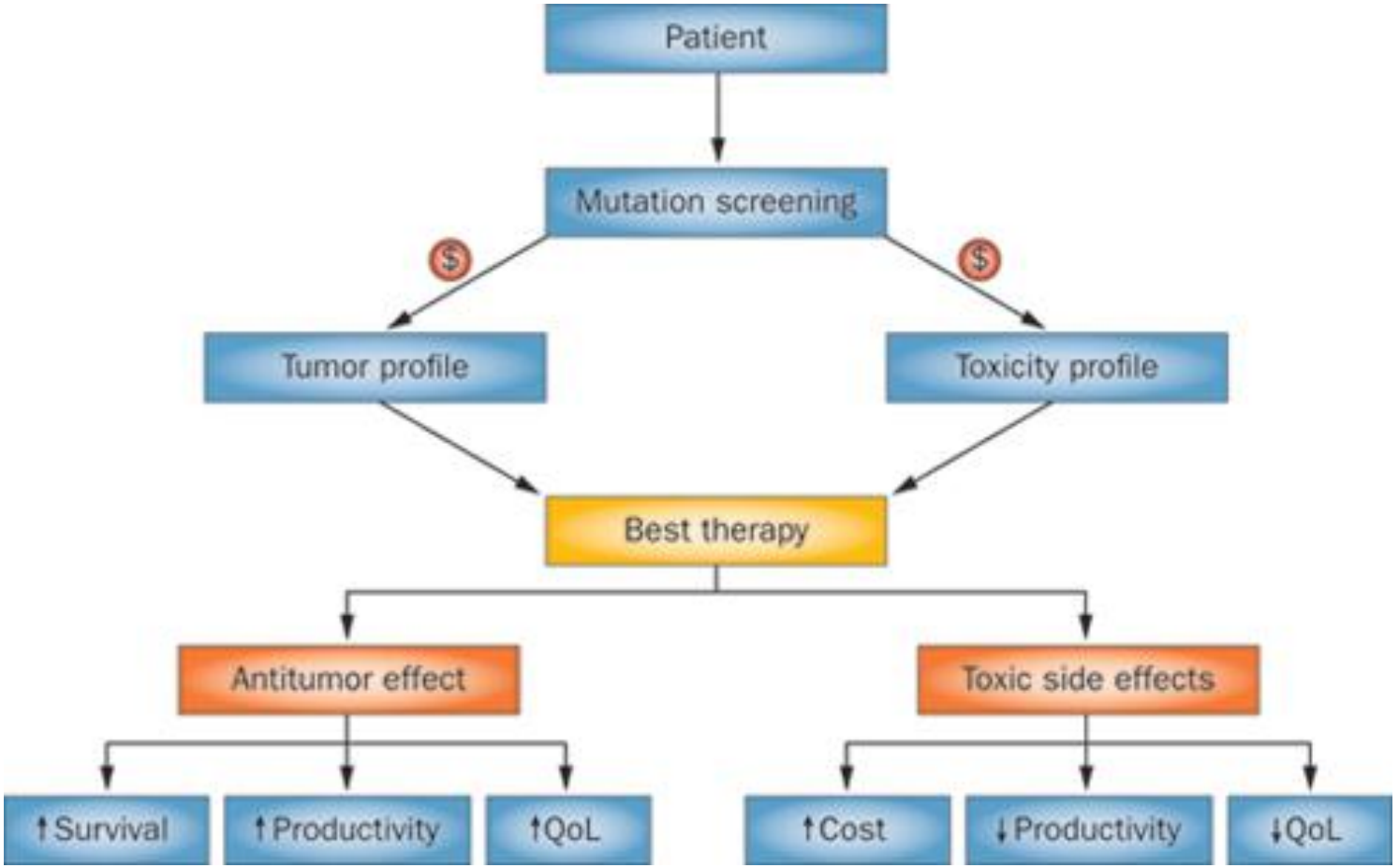
- Topical high-potency corticosteroids
  - Dexamethasone (0.1 mg/ml)
  - Clobetasol gel (0.05%)
- Topical nonsteroidal anti-inflammatory
  - Amlexanox 5% oral paste
- Topical anesthetic
  - Viscous lidocaine (2%)

Treatment for mTOR inhibitor-associated esophageal ulcers

- High-dose prednisone or prednisolone
- Treatment for Grade 2 or higher mIAS
- Dose reduction of mTOR inhibitor (?)

Pilotte AP et al. *Clin J Oncol Nurs*. 2011;15:E83-89

# PCM: Increased tumour control and reduced toxicity



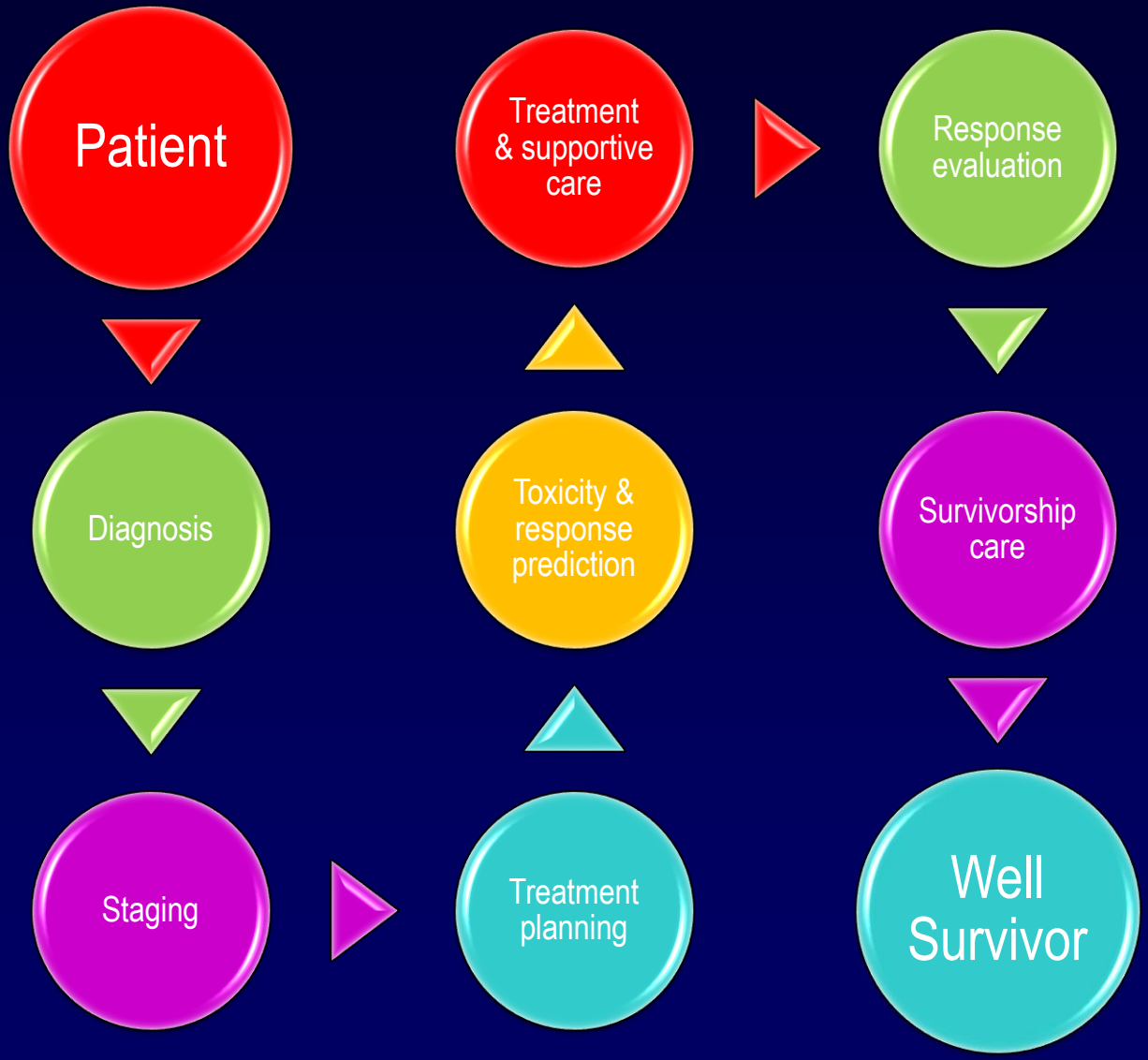

nature REVIEWS CLINICAL ONCOLOGY

Keefe, D. *Nat. Rev. Clin. Oncol.* doi:10.1038/nrclinonc.2011.192

# Key Points

1. GI toxicity  is a major toxicity
2. It rarely occurs in isolation
3. Targeted anti-cancer therapies cause GI toxicity by new mechanisms
4. Applied genomics allows genome-wide risk prediction tool development and promises true personalized cancer medicine
5. Optimization of clinical and health care economic outcomes requires
    - Evaluation of the literature
    - Development of Evidence-Based Guidelines
    - Dissemination of guidelines
    - Education
    - EVALUATION of outcomes

# Ideal Situation



# New Gordon Research Conference

Mucosal Health & Disease

9-14 June 2013

Stonehill College

Easton, Massachusetts USA

www.grc.org/programs.aspx?year=2013&program=mucosal

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