INFLAMMATION & CANCER

Tissue damage
Tumour promotion
Chronic infection
Chronic inflammation

Cytokines and chemokines

DNA damage
Bypass p53
Growth stimulation
Enhanced survival
Angiogenesis
Subversion of immunity
Enhanced invasion
**INFLAMMATION & CANCER: BACK TO VIRCHOW?**

**MOTIVATION**

**WOUND HEALING**

**INFLAMMATION**

**TAM & TNF**

**DC**

**CYTOKINES**

**METASTASIS**

**METABOLISM**

**THERAPEUTICS**

**THE END**

(*HUGO VOGEL 1861*)

**Motivation**

Inflammation & cancer: back to Virchow?

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Wound healing

DC

TAM & TNF

Cytokines

Metastasis

Metabolism

Therapeutics

The end
## MOTIVATION

<table>
<thead>
<tr>
<th>WOUND HEALING</th>
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</table>

- **What is the relationship between wound-healing & cancer development?**
- **Malignant tumours often develop at sites of chronic injury**
- **Tissue injury has an important role in malignant disease pathogenesis**
- **Chronic inflammation being the most important risk factor**

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**Cancer as an Overhealing Wound**

**Lets Go!**

Breast cancer
CANCER AS AN OVERHEALING WOUND

<table>
<thead>
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<th>MOTIVATION</th>
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<tbody>
<tr>
<td></td>
<td>Common cellular and molecular mechanisms are active in wounds and in cancer tissue</td>
</tr>
<tr>
<td></td>
<td>Sir Alexander Haddow suggested that “tumour production is a possible overhealing”</td>
</tr>
<tr>
<td></td>
<td>Harold Dvorak postulated that “tumors are wounds that do not heal”</td>
</tr>
</tbody>
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 Motivation

- Wound Healing
- Inflammation
- TAM & TNF
- DC
- Cytokines
- Metastasis
- Metabolism
- Therapeutics
- The End
Wounds vs. Tumours

**Motivation**

- **Wound Healing**
- **Inflammation**
- **TAM & TNF**
- **DC**
- **Cytokines**
- **Metastasis**
- **Metabolism**
- **Therapeutics**
- **The End**

**Box 1 | Molecular parallels between wound healing and cancer**

Microarray analyses have provided insights into the molecular similarities and differences between tissue repair and cancer:

- The genes that are regulated in fibroblasts following serum treatment encode proteins that are required for wound repair.
- The gene-expression pattern of serum-treated fibroblasts strongly resembles that of human carcinomas. Remarkably, tumours with a gene-expression pattern that is similar to the serum-activated programme of fibroblasts were significantly more likely to progress to metastasis and cause death. Thus, the presence of a gene-expression signature that is similar to the one in early wounds allows a prediction of poor prognosis. In these tumours, the ‘wound’ genes are expressed by the tumour cells themselves and by stromal cells.
- Most of the genes that are expressed in a model of renal regeneration and repair and in renal cancer were concordantly regulated. The genes regulated in opposing directions in wounds and tumours (for example, upregulated in wounds and downregulated in tumours and vice versa) encode proteins that are required for morphogenesis or glucose metabolism. The identification of the glucose metabolism genes reflects the fact that most tumours produce ATP through anaerobic glycolysis (a process known as the Warburg effect).
- Genes were identified that are differentially expressed in the hyperproliferative epithelium of healing skin wounds compared with normal epidermis, and most of them were regulated in a similar manner in epithelial skin cancer. Genes regulated in opposing directions in wounds and tumours are associated with the irreversible loss of the differentiation and growth control capacity and with the invasiveness of malignant epidermal cancer cells.

It will be interesting to compare the gene-expression pattern of wounds at a late stage of repair with that of tumours. This comparison might reveal further differences, as wounds heal at this stage, whereas cancers continue to grow and metastasize. The genes that are differentially expressed at this stage might provide important insights into the mechanisms that are involved in the shutdown of the repair response and could represent promising targets for tumour therapy.
The different phases of wound repair

**MOTIVATION**

**WOUND HEALING**

**INFLAMMATION**

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**METABOLISM**

**THERAPEUTICS**

**THE END**

*Let's Go!*

*Schäfer et al. 2008*
FIBRIN IN WOUNDS AND TUMOURS

WOUND HEALING

INFLAMMATION

TAM & TNF

DC

CYTOKINES

METASTASIS

METABOLISM

THERAPEUTICS

THE END

(SCHÄFER ET AL. 2008)
PARALLELS BETWEEN WOUNDS & CANCER

MOTIVATION

WOUND HEALING

INFLAMMATION

TAM & TNF

DC

CYTOKINES

METASTASIS

METABOLISM

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THE END

(SCHAFFER ET AL. 2008)
**WOUND HEALING vs INVASIVE TUMOUR**

**MOTIVATION**

**WOUND HEALING**

**INFLAMMATION**

**TAM & TNF**

**DC**

**CYTOKINES**

**METASTASIS**

**METABOLISM**

**THERAPEUTICS**

**THE END**

(COUSSENS ET AL. 2002)
# Angiogenesis, Wounds & Cancer

## Motivation

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## (Schäfer et al. 2008)

![Diagram](schaefer_2008_diagram.png)

- **Epithelial cells**
  - VEGFA
  - HGF, PLGF
  - GM-CSF, MMPs
- **Immune cells**
  - MMPs
  - TSP1
  - VEGFA
  - VEGFC
- **Blood vessel**
  - VEGFA
  - HGF, FGF2
  - TSP1, MMPs

- **Images**
  - Image a:微血管
  - Image b: K14, PECAM1
  - Image c: HE, G

**Let's Go!**

Breast cancer

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Tumours are wounds that do not heal (Mueller et al. 2004)

Motivation

Wound Healing

Inflammation

Tam & TNF

DC

Cytokines

Metastasis

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Breast Cancer

(Mueller et al. 2004)
THE TUMOUR MICROENVIRONMENT: THE ROLE OF INFLAMMATION IN CANCER

Motivation

Wound healing

Inflammation

TAM & TNF

DC

Cytokines

Metastasis

Metabolism

Therapeutics

The End

(ALBINI ET AL. 2007)
CANCER RELATED INFLAMMATION

MOTIVATION
WOUND HEALING
INFLAMMATION
TAM & TNF
DC
CYTOKINES
METASTASIS
METABOLISM
THERAPEUTICS
THE END

New discovery in 2008

(THTTP://UNIVERSE-REVIEW.CA/F11-MONOCELL.HTM)
INFLAMMATION TYPES PROMOTING CANCER

1. Therapy-induced inflammation
   - Tumor re-emergence
   - Resistance to therapy

2. Tumor development
   - Antigen presentation
   - Cancer cell killing

3. Inflammation caused by environmental and dietary exposure
   - Mutations
   - Genomic instability
   - Tumor promotion
   - Angiogenesis

4. Tumor-associated inflammation
   - Mutations
   - Genomic instability
   - Tumor promotion
   - Angiogenesis

5. Chronic inflammation
   - Infection
   - Autoimmunity

**MOTIVATION**

WOUND HEALING

INFLAMMATION

TAM & TNF

DC

CYTOKINES

METASTASIS

METABOLISM

THERAPEUTICS

THE END

*Grivennikov et al. 2010*
STATISTICALLY DERIVED MODELS

MOTIVATION
WOUND HEALING
INFLAMMATION
TAM & TNF
DC
CYTOKINES
METASTASIS
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THE END

(GRIVENNIKOV ET AL. 2010)
TUMOUR-ASSOCIATED MACROPHAGES

Motivation

Wound healing

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(SHUNYAKOV ET AL. 2004)
TUMOUR NECROSIS FACTOR IN MICROENVIRONMENT

1. MOTIVATION
2. WOUND HEALING
3. INFLAMMATION
4. TAM & TNF
5. DC
6. CYTOKINES
7. METASTASIS
8. METABOLISM
9. THERAPEUTICS
10. THE END

Let's Go!

(Balkwill et al. 2009)
IMMATURE DCs INDUCE TOLERANCE

MOTIVATION
WOUND HEALING
INFLAMMATION
TAM & TNF
DC
CYTOKINES
METASTASIS
METABOLISM
THERAPEUTICS
THE END

(LANCHEREAU ET AL. 2005)
Mature DCs induce immunity

Motivation

Wound Healing

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Banchereau et al. 2005
Inflammation & Neoplastic Progression

Motivation
Wound Healing
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DC
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Metastasis
Metabolism
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Let's Go!

(Coussens et al. 2002)
**PROINFLAMMATORY CYTOKINES**

**MOTIVATION**

**WOUND HEALING**

**INFLAMMATION**

**TAM & TNF**

**DC**

**CYTOKINES**

**METASTASIS**

**METABOLISM**

**THERAPEUTICS**

**THE END**

(LIN ET AL. 2007)
Chemokine Gradient in Cancer

**Motivation**

- Wound healing
- Inflammation
- TAM & TNF
- DC

**Cytokines**

- Metastasis
- Metabolism
- Therapeutics

**The End**

*(Balkwill et al. 2004)*

Let's Go!
MECHANISMS OF ACTION OF CYTOKINES IN TUMOURS

MOTIVATION
WOUND HEALING
INFLAMMATION
TAM & TNF
DC
CYTOKINES
METASTASIS
METABOLISM
THERAPEUTICS
THE END

(BALKWILL ET AL. 2001)
INFLAMMATION AND METASTASIS

MOTIVATION
WOUND HEALING
INFLAMMATION
TAM & TNF
DC
CYTOKINES
METASTASIS
METABOLISM
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Let's Go!

(STEEG ET AL. 2003)
**OMETATION & AVOIDANCE OF IMMUNOSURVEILLANCE**

**FIGURE 1.**
Tryptophan, kynurenine, and quinolinic acid

IDO converts tryptophan to kynurenine, an NMDA receptor antagonist. This reduces tryptophan availability for serotonin synthesis. Microglia activated by inflammatory mediators can convert tryptophan to quinolinic acid, an NMDA agonist. Therefore, pro-inflammatory mediators favor the production of quinolinic acid, while anti-inflammatory mediators inhibit synthesis of quinolinic acid. Decreased serotonin availability and excessive glutamate receptor agonism have been implicated in depression. Depression associated with IFN-α treatment may occur because of interference with this pathway, and selective serotonin reuptake inhibitors, such as paroxetine, are, therefore, efficacious in treating depression caused by IFN-α. The word neurotoxicity denote consequences of excess excitatory amino acid levels, however, neurotoxicity has not been unequivocally demonstrated in depression.

NMDA=N-methyl-D-aspartate; Th1 helper cell; IL=interleukin; IDO=indoleamine 2,3-dioxygenase; IFN=interferon; TNF=tumor necrosis factor; 5-HIAA=5-hydroxyindoleacetic acid.

Therapy-Induced Inflammation—Friend or Foe?

Motivation

Wound Healing

Inflammation

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(Grivennikov et al. 2010)
Implications For Therapeutics (Balkwill et al. 2010)

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Breast cancer

Immunosuppression?

Malignant cell

Lymphocyte

TNFR1

• Proliferation
• DNA damage
• EMT
• Survival

TNF and other cytokines

• M2 phenotype
• Myeloid–endothelial phenotype
• ECM remodeling

• Increase in primary tumor growth and metastases
• Leukocyte infiltrate
• Angiogenesis
• Pleural effusion
• Immune evasion and resistance to chemotherapy
Thank you