Translational Systems Immunology

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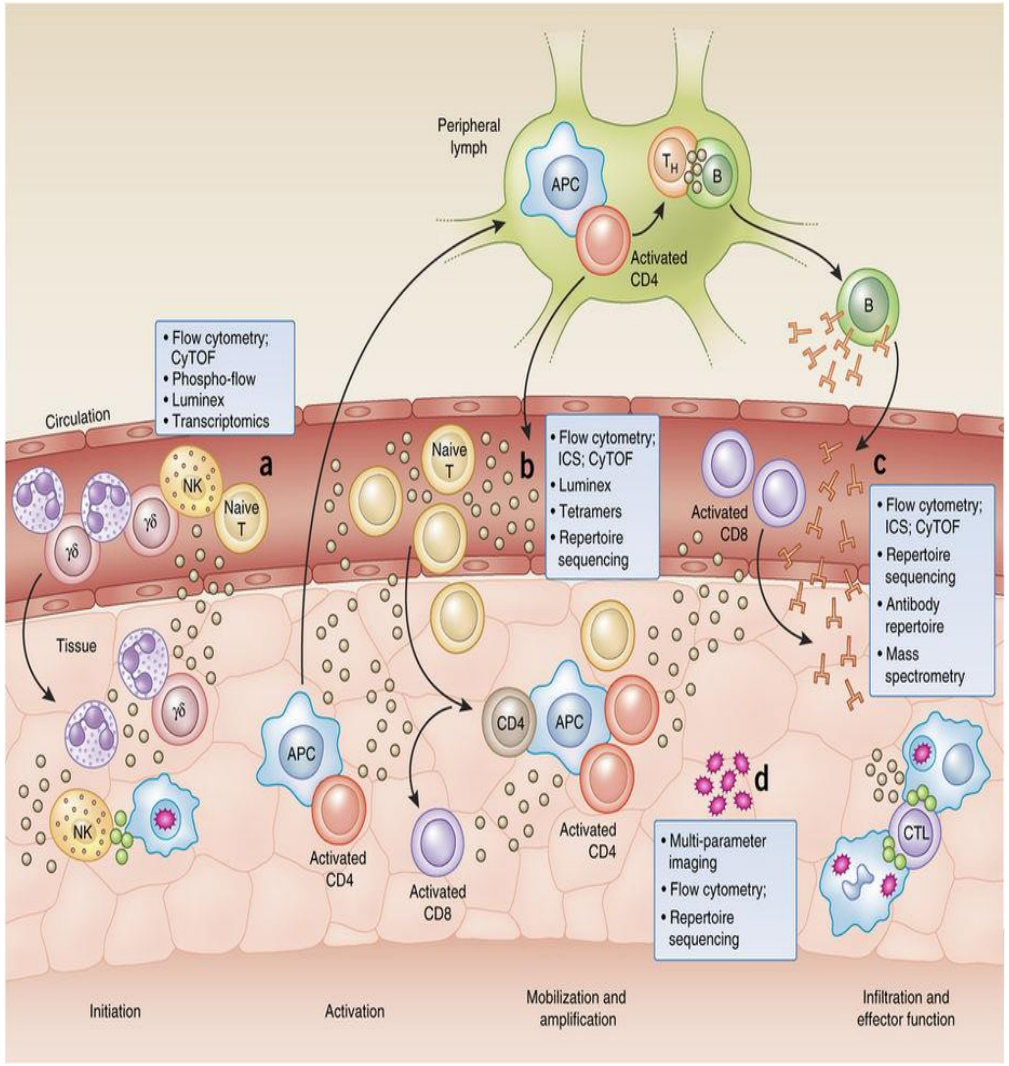
- Why?

  The immune system is too complicated to proceed in the usual one-variable-at-a-time manner

  $$ alone won't result in success

Figure 1 : Tools of the trade: a systems-immunology view.

From: Systems immunology: just getting started



While many of the previously mentioned studies suggest potential targets to control cellular behavior, a recent study demonstrates the full power of this approach by analyzing a network model, identifying the mechanism to target, and then developing and testing a monoclonal antibody against the target. Schoeberl et al. [63] utilized an ErbB network model incorporating ligand binding, receptor dimerization/internalization/degradation/recycling, and signaling events through the PI3K axis. Sensitivity analysis determined that ErbB3 was the most important node leading to AKT activation; this was an unexpected result as ErbB3 does not have kinase activity, and is not frequently mutated or overexpressed in tumors. This analysis clearly demonstrated the importance of looking across multiple pathways—while the ultimate result was a single target, the mechanism supporting the importance of ErbB3 in tumor cell proliferation is the combinatorial interaction between multiple ligands and receptors that is influenced by ErbB3. Subsequent to the identification of ErbB3 as a drug target, the group returned to their mass-action kinetic model to find the optimal kinetic and biochemical properties of an inhibitor against ErbB3; this study guided the development of MM-121, a fully human IgG2 monoclonal antibody against ErbB3, which is currently in phase II clinical trials [63].

The rapid development of targeted inhibitors and the highly heterogeneous nature of tumors have led to an increased interest in designing combinatorial therapeutic strategies [83]. By employing a network-level perspective and targeting multiple pathways simultaneously, it may be possible to overcome pathway cross-talk and redundant mechanisms that are thought to be responsible for the modest responses observed in trials of targeted therapies [84]. Compensation in other pathways in response to treatment with targeted inhibitors has been observed both experimentally and in model simulations. For example, a mass-action kinetic model of IGF receptor signaling in breast cancer cells was able to capture the effect of treatment with a MEK inhibitor [85]. Due to pathway interactions, this resulted in the expected decrease in phosphorylated ERK, but also an unexpected activation of the PI3K/AKT pathways. Observations such as this illustrate the need to simultaneously target multiple pathways for cancer therapy. Additionally, multiscale models such as those developed for the ErbB network may allow for therapeutic strategies to be tested in an *in silico* environment that mimics the cellular heterogeneity of a tumor [46].

- Why not?

  Systems biology has not been very impactful in the past

Limitations of many systems biology studies

- Global-
  Trying to understand full system interactions by modeling publically available datasets

- Anti reductionist

- Not focused on translational objectives

Christophe Benoist
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A *Plaidoyer* for 'Systems Immunology'

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Summary: A complete understanding of the immune system will ultimately require an integrated perspective on how genetic and epigenetic entities work together to produce the range of physiologic and pathologic behaviors characteristic of immune function. The immune network encompasses all of the connections and regulatory associations between individual cells and the sum of interactions between gene products within a cell. With 30 000+ protein-coding genes in a mammalian genome, further compounded by microRNAs and yet unrecognized layers of genetic controls, connecting the dots of this network is a monumental task. Over the past few years, high-throughput techniques have allowed a genome-scale view on cell states and cell- or system-level responses to perturbations. Here, we observe that after an early burst of enthusiasm, there has developed a distinct resistance to placing a high value on global genomic or proteomic analyses. Such reluctance has affected both the practice and the publication of immunological science, resulting in a substantial impediment to the advances in our understanding that such large-scale studies could potentially provide. We propose that distinct standards are needed for validation, evaluation, and visualization of global analyses, such that in-depth descriptions of cellular responses may complement the gene/factor-centric approaches currently in favor.

CROSSING THE VALLEY OF DEATH

A chasm has opened up between biomedical researchers and the patients who need their discoveries. **Declan Butler** asks how the ground shifted and whether the US National Institutes of Health can bridge the gap.

"NIH stands for the National Institutes of Health, not the National Institutes of Biomedical Research, or the National Institutes of Basic Biomedical Research." This jab, by molecular biologist Alan Schechter at the NIH, is a pointed one. The organization was formally established in the United States more than half a century ago to serve the nation's public health, and its mission now is to pursue fundamental knowledge and apply it "to reduce the burdens of illness and disability". So when employees at the agency have to check their name tag, some soul searching must be taking place.

There is no question that the NIH excels in basic research. What researchers such as Schechter are asking is whether it has neglected the mandate to apply that knowledge. Outside the agency too there is a growing perception that the enormous resources being put into biomedical research, and the huge strides made in understanding disease mechanisms, are not resulting in commensurate gains in new treatments, diagnostics and prevention. "We are not seeing the breakthrough therapies that people can rightly expect," says Schechter, head of molecular biology and genetics at the National Institute of Diabetes and Digestive and Kidney Diseases in Bethesda, Maryland.

Medical-research agencies worldwide are experiencing a similar awakening. Over the past 30 or so years, the ecosystems of basic and clinical research have diverged. The pharmaceutical industry, which for many years was expected to carry discoveries across the divide, is now hard pushed to do so. The abyss left behind is sometimes labelled the 'valley of death' — and neither basic researchers, busy with discoveries, nor physicians, busy with patients, are keen to venture there. "The clinical and basic scientists don't really communicate," says Barbara Alving, director of the NIH's National Center for Research Resources in Bethesda.

E. MILLER

Alving is a key part in the NIH's attempt to bridge the gap with 'translational research'. Director Elias Zerhouni made this bridge-building a focus in his signature 'roadmap' for the agency, announced in 2003 (see *Nature* 425, 438; 2003). Spearheading the NIH effort will be a consortium of 60 Clinical and Translational Science Centers (CTSCs) at universities and medical centres across the country, which will share some US$500 million annually when they are all in operation by 2012. Late last month, the NIH doled out the most recent grants in

Translational Research

- Not just making a biological measurement on a patient

Lee Nadler

- “A translational researcher is someone who takes something from basic research to a patient and measures an endpoint in a patient.”

GW Sledge
JNCI 2004

- “Translational research – that precarious bridge between the laboratory and the clinic – is, in Shakespeare’s words, a ‘custom more honored in the breach than in the observance’.”
- “Preclinical studies and metastatic phase II trials rarely lead to anything useful for patients: they are wasteful in a profound and disturbing sense, far beyond the inherent messiness of science. I suspect this reflects an inherent lack of vision on the part of both laboratory and clinical researchers. Designing a sequential series of experiments, both laboratory and clinical, that lead intentionally to proof-of-concept adjuvant trials is all too rare.”

It’s not uni-directional

- For most, translational medicine describes a uni-directional effort to test in humans novel therapeutic strategies developed through experimentation.
- This would suffice if experimental models were representative of human pathology.
- Translational medicine is a two-way street

It takes a trans-disciplinary team

- Laboratory-based investigators
  - Pre-clinical target validation
  - Assessment of biologic markers in situ
  - Measurement of surrogate endpoints
- Clinical investigators
  - Plan and investigate the experiments
  - Medical oncologists, surgeons, radiologists, pathologists, molecular pathologists, statisticians, research nurses, data managers

- Sharing results is not deep collaboration

Translational Research in the Pharmaceutical Industry

D. O'Connell and David Roblin

- "Communication between basic and clinical scientists is rare and sporadic…
- Translational drug investigators need to draw on the expertise of various discovery, preclinical safety and clinical groups. To that end, it is crucial in drug development to have dedicated translational groups to implement translational research strategy at the therapeutic and project levels.
- Sustaining a vigorous rate of transfer of basic findings into clinical application requires a stable and well trained cadre of 'translational' drug investigators to patrol the borders of the basic-clinical interface."

If it's the atomic bomb you want, start recruiting for the Manhattan Project. But if it's atomic theory you're after, look for the lone thinker who comes up with $e=mc^2$

Gerald Weissmann, FASEB Journal 19:1761, 2005

- We need both
  - The bomb would not have been developed without a Manhattan product oriented project
  - The current level of mortality and suffering from cancer creates an urgent need for greater progress
  - Are there translational opportunities for which the importance and chance of success are sufficiently great to warrant greater focus and prioritization than the current NIH approach provides?
- Successful translational research has usually been based on incomplete understanding of biological mechanisms
  - We probably do not fully understand the pathogenesis of any human cancer but partial understanding has been sufficient for some successes
    - ER, BCR-ABL, HER2, VEGF

Moving Forward

- Deep collaborations driven by important patient needs and key translational opportunities
  - Focus on specific goals, not infrastructure
  - Establishing the tight partnerships, resources and management support needed to pursue the goals
  - Critical assessment of progress

Systems Immunology Approach for Improving T Cell Cancer Therapy

- Cells
  - Tumor cells
  - Immune cells
    - Dendritic cells
    - CD8 T cells
    - CD4 T cells
    - Regulatory T cells
  - Stromal cells
- Cytokines

- Cell states
  - Tumor cells
    - MHC expression
    - Neo-antigen repertoire
    - ϒ-IFN pathway status
  - CD8 T cells
    - Location
    - Maturity
    - CD25 signaling
    - CTLA signaling
    - PD1 signaling

- Interactions and changes of cell state

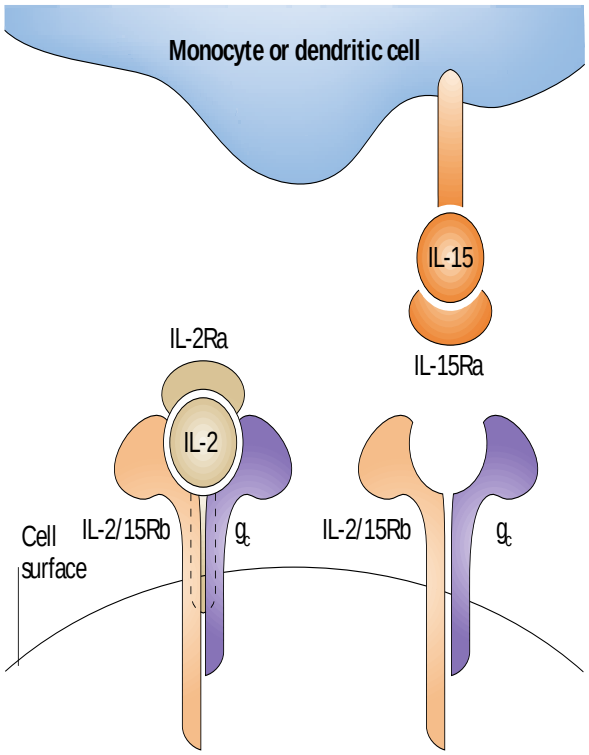

Figure 2 | **The mode of interaction of interleukin-2 and interleukin-15 with the subunits of their receptors.** Interleukin-2 (IL-2) is a secreted cytokine that binds pre-formed high-affinity heterotrimeric receptors that comprise the IL-2 receptor a-chain (IL-2Ra), IL-2/15Rb and the common cytokine-receptor g-chain (γ_c). By contrast, IL-15 is a membrane-associated molecule that induces signalling at the immunological synapse between antigen-presenting cells and natural killer (NK) cells or $CD8^+$ T cells. IL-15Ra on the surface of monocytes or dendritic cells presents IL-15 in trans to cells that express IL-2/15Rb and γ_c alone, thereby allowing signalling through these complexes.

- State transition equations
  - CD8 cell -> 2 CD8 cells depending on [IL2]
  - CD8 with activated CD25, activated TCR and non-inhibited CTLA4 secrets IFN-ϒ

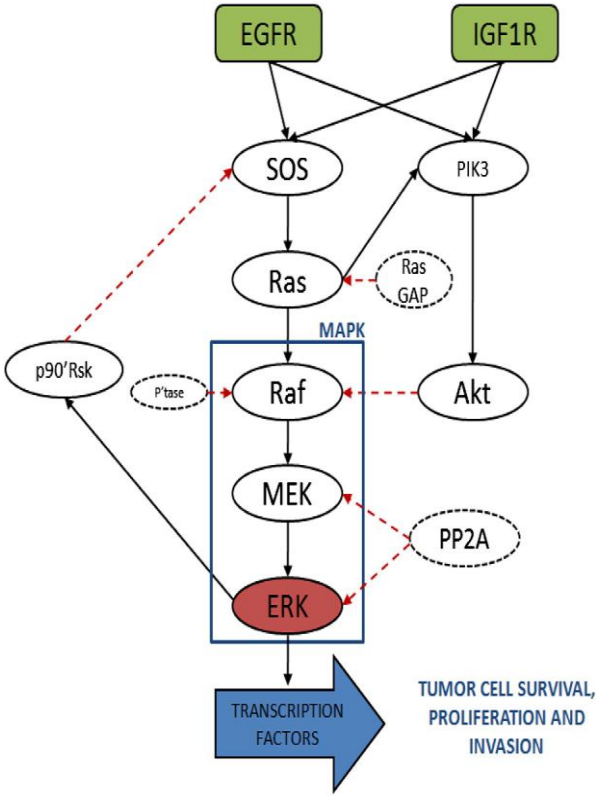

Fig. 1. Schematic of EGFR and IGF1R pathways.

Table 1
Model reactions and kinetic laws.

Kinetics reaction	Kinetic law
$EGFR^* + SOS \xrightarrow{k} SOS^* + EGFR^*$	EMM
$SOS^* + Ras \xrightarrow{k} Ras^* + SOS^*$	EMM
$p90Rsk^* + SOS^* \xrightarrow{k} SOS + p90Rsk^*$	EMM
$IGF1R^* + SOS \xrightarrow{k} SOS^* + IGF1R^*$	EMM
$PIK3CA + IGF1R^* \xrightarrow{k} PIK3CA^* + IGF1R^*$	EMM
$PIK3CA + EGFR^* \xrightarrow{k} PIK3CA^* + EGFR^*$	EMM
$Akt + PIK3CA^* \xrightarrow{k} Akt^* + PIK3CA^*$	EMM
$MEK^* + ERK \xrightarrow{k} ERK^* + MEK^*$	EMM
$Akt^* \xrightarrow{k} Akt$	Mass action
$ERK^* + PP2A \xrightarrow{k} ERK + PP2A$	EMM
$PIK3CA + Ras^* \xrightarrow{k} PIK3CA^* + Ras^*$	EMM
$Ras^* + Raf \xrightarrow{k} Raf^* + Ras^*$	EMM
$Raf^* + MEK \xrightarrow{k} MEK^* + Raf^*$	EMM
$Akt^* + Raf^* \xrightarrow{k} Raf + Akt^*$	EMM
$RasGap^* + Ras^* \xrightarrow{k} Ras + RasGap^*$	EMM
$PP2A + MEK^* \xrightarrow{k} MEK + PP2A$	EMM
$PIK3CA^* \xrightarrow{k} PIK3CA$	Mass action
$RafPP + Raf^* \xrightarrow{k} Raf + RafPP$	EMM
$p90Rsk + ERK^* \xrightarrow{k} p90Rsk^* + ERK^*$	EMM
$p90Rsk^* \xrightarrow{k} p90Rsk$	Mass action

System Evolution

- Concentrations of cytokines and cell types and their states evolve over time according to the system equations and initial values of the parameters

Research article

IL-12 triggers a programmatic change in dysfunctional myeloid-derived cells within mouse tumors

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Solid tumors are complex masses with a local microenvironment, or stroma, that supports tumor growth and progression. Among the diverse tumor-supporting stromal cells is a heterogeneous population of myeloid-derived cells. These cells are alternatively activated and contribute to the immunosuppressive environment of the tumor; overcoming their immunosuppressive effects may improve the efficacy of cancer immunotherapies. We recently found that engineering tumor-specific $CD8^+$ T cells to secrete the inflammatory cytokine IL-12 improved their therapeutic efficacy in the B16 mouse model of established melanoma. Here, we report the mechanism underlying this finding. Surprisingly, direct binding of IL-12 to receptors on lymphocytes or NK cells was not required. Instead, IL-12 sensitized bone marrow–derived tumor stromal cells, including $CD11b^+F4/80^{hi}$ macrophages, $CD11b^+MHCII^{hi}CD11c^{hi}$ dendritic cells, and $CD11b^+Gr\text{-}1^{hi}$ myeloid–derived suppressor cells, causing them to enhance the effects of adoptively transferred $CD8^+$ T cells. This reprogramming of myeloid-derived cells occurred partly through IFN-γ. Surprisingly, direct presentation of antigen to the transferred $CD8^+$ T cells by tumor was not necessary; however, MHCI expression on host cells was essential for IL-12–mediated antitumor enhancements. These results are consistent with a model in which IL-12 enhances the ability of $CD8^+$ T cells to collapse large vascularized tumors by triggering programmatic changes in otherwise suppressive antigen-presenting cells within tumors and support the use of IL-12 as part of immunotherapy for the treatment of solid tumors.

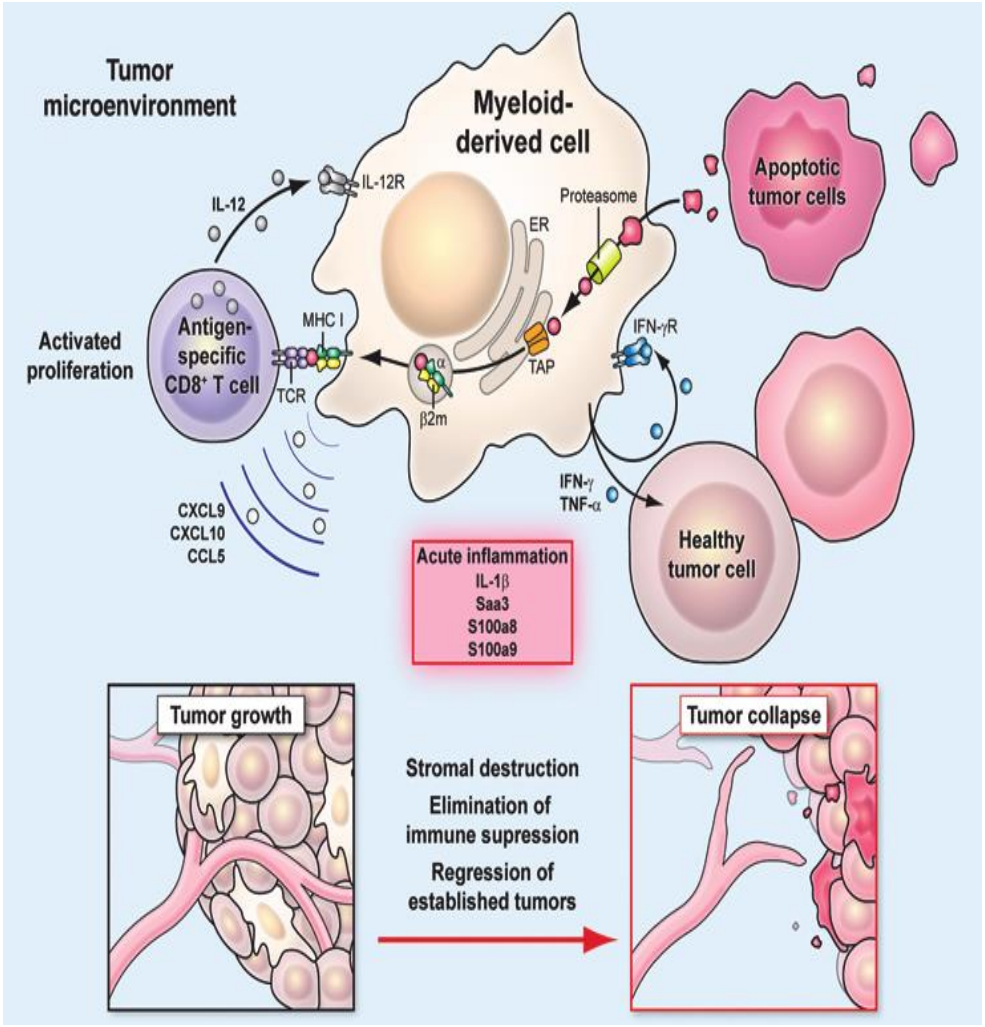

Figure 9

Schematic diagram summarizing the proposed mechanism for tumor destruction induced by IL-12. Myeloid-derived cells within the tumor microenvironment are sensitized by IL-12 to create an acute inflammatory environment and improve the ability of antigen-specific $CD8^+$ T cells to collapse large established tumors.

Parameters

- Specified based on measurements
- Optimized based on simulated evolution with other measurements

Modeling Process

- Performed using drag & drop web app by collaborating immunotherapists

In-silico Experiments

- Performed to find interventions or combinations of interventions predicted to enhance tumor lysis or to better understand system interactions

- Iterative process of model modification, measurement, and in-silico simulation

- Leading to improved tumor lysis

- Thank you