Translational Challenges in Biomedical Research

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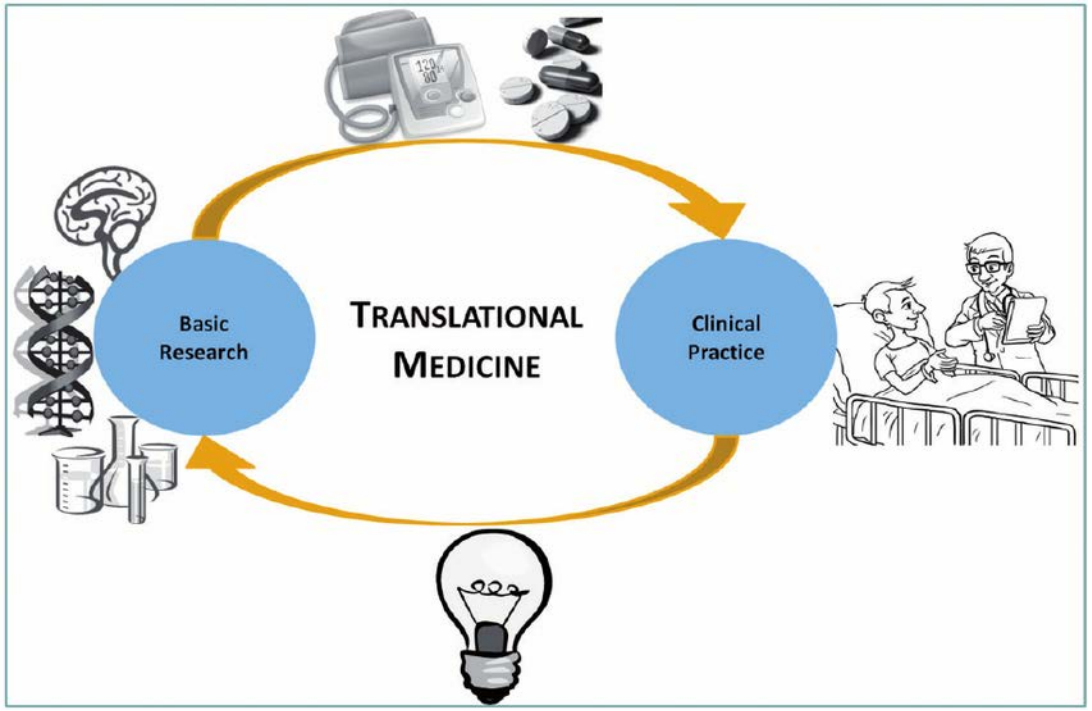
Translational Medicine

- Term appears regularly in the literature from 2003, now over 40 journals and various societies
- 2004 NIH Roadmap (USA) featured “translational research.” Now NIH funds 27 Institutes and centers including the National Center for Advancing Translational Sciences in the USA. Europe has EATRIS and the UK has ?
- The focus is on “bench to bedside and back” (T1) and interdisciplinary collaborative research (see Woolf 2008)
- “The heart of translational research resides in Phase I trials” (Marincola 2003)
- Donald Berwick (2005) claims that we have “overshot the mark” with EBM and created intellectual hegemony. Translational medicine restores the “pragmatic” reasoning needed in medical science.

The term “translational medicine” is a new (and metaphorical) name for an old strategy



The strategy is going from basic research—reasoning and experimenting with **models--**to implementing aspects of the models in clinical practice**.** And making observations in clinical practice that can be taken back to the lab.

(The alternative is serendipity)

It should be distinguished from “evidence-based medicine” which can only be done after translational work produces plausible suggestions about possible interventions.

What is a model?

Something to think with

An essential tool of scientific research

(includes theories, but also non-mental models such as animal models of human diseases).

Used to suggest possible interventions.

Simplification or idealization or convenient or ethical representation of the thing we are trying to understand.

It can be an equation, a mental model, a physical model, an animal model, an in vitro model.

Examples

- There are 188 different “mouse models” of Alzheimer disease=188 different kinds of genetic modifications each intended to model symptoms of Alzheimer
- There are cell models of cystic fibrosis using cells taken from patients that study their sodium channel transport with various added modulators/potentiaters
- There are several (different) mental models of cancer each of which lead to different suggestions about treatment (strategic invasion, a breakdown in function, a process of naturalselection, a genetic disease, an infectious disease (in some cases), a stem cell disorder, a metabolic disorder, a disease of tissue organization, a natural consequence of aging, an environmental disease, and/or a developmental regression. See Plutynski (2018)

The Challenge of Translational Medicine

- To use a model as the basis for creating a clinical intervention
- An intervention that works in vitro or in animal studies may not work for humans.
- The reason for this is that models typically simplify and/or idealize disease states in humans
- Can we figure out in advance whether the translation will work? My answer: rarely, because most diseases are SCOTCH diseases about which we know little.
- Even in cases that we think we understand well (e.g. convalescent plasma for Covid-19, cement for osteoporotic fractures in the spine) interventions frequently fail.

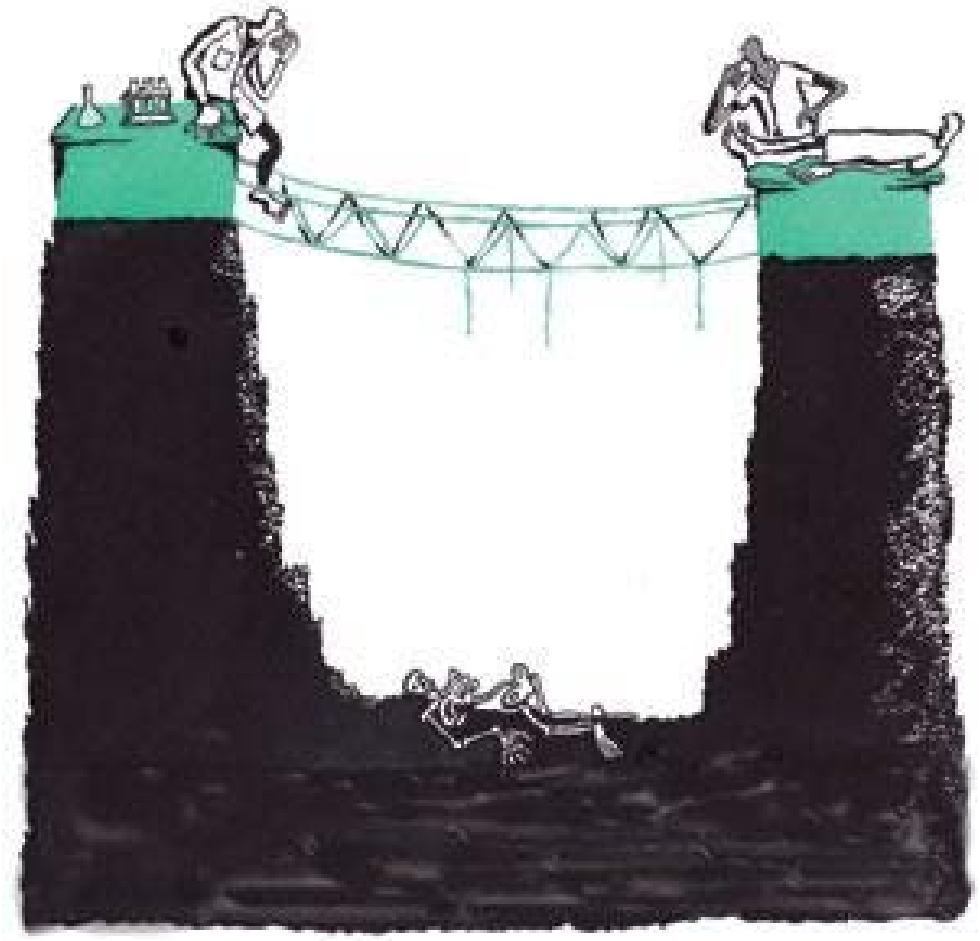
Three common features of MOST diseases

(cancer, amyloid diseases, cardiovascular diseases, rheumatic diseases, auto-immune diseases, most infectious diseases….even some monogenic diseases such as cystic fibrosis)

1. Complexity (The mechanisms underlying diseases are complex)
2. Heterogeneity (The mechanisms underlying diseases are variable)
3. Significant Change Over Time (diseases sometimes progress, sometimes relapse and remit, sometimes both)

= “SCOTCH” diseases

Crossing the “Valley of Death” (= “translational gap”) (from Nature 2008)



The “valley of death”: casualties

- In general, 90-95% of drugs entering clinical trials fail (exact figures depend on measures)
- Early efforts to replace faulty genes with healthy ones using viral vectors in monogenic diseases typically did not work (e.g. adeno-associated virus for cystic fibrosis) and sometimes harmed (adenoviral vector for OTC deficiency and Jesse Gelsinger’s death in 1999)
- A succession of early treatments for Covid-19, including hydroxychloroquine (in vitro anti-viral activity), azithromycin (anecdotal?), convalescent plasma (prior successes with other diseases and understanding of the mechanism of action), lopinavir and ritonavir (anti-viral), colchicine (anti-inflammatory).

The “valley of death”: escapees (drug successes)

- Success of CRISPR-Cas9 in vivo gene editing for transthyretin amyloidosis (Julian Gillmore et al. 2021)
- Promise of Trikafta in cystic fibrosis (many steps, important roles of Cystic Fibrosis Foundation, Vertex Pharmaceuticals)
- Historic examples: development of insulin for diabetes (dog model, after much fiddling, role of Eli Lilly company), development of penicillin for infections.
- Remdesivir for Covid-19

What to do about the valley of death

- Discover so much about the model and the thing modeled that there is no missed mechanism or detail and therefore no room for error. (Martin Wheling and a “translatability score”). Downside: we may be waiting a long time (if ever) for this.
- **Try again, using educated guesses; expect a high failure rate and hope to be lucky.** This requires flexibility, imagination, willingness to try out different approaches, knowing when to give up, assembling a group of researchers and clinicians with diverse talents: both scientific challenges and social/institutional/communicative challenges

1. Recommendations for Addressing Scientific Challenges

- Use partial knowledge and available models to make suggestions for intervention
- Tinker until get some kind of controllable effect in some kind of model.
- Try to extend intervention to humans—again, tinkering ("bench to bedside and back"). Phase 1 (safety) and 2 (initial data) clinical trials
- When effect looks robust and safe, design stage 3 clinical trials.

2. Social/Institutional/Communicative Challenges

Science is socially produced knowledge

Robert K. Merton, 1910-2003

- 1942 paper, “A note on science and technology in a democratic order”
- Described “***ethos of science***”:
  1. Universality
  2. Communality
  3. Disinterestedness
  4. Organized skepticism

Some current problematic (non-Mertonian) social/institutional/communicative features of science

- Lack of neutrality ("falling in love" with one's model, despite translational failures)
- Proprietary data (for commercial and competitive reasons)
- Commercial interests (sponsorship of research, ownership of journals)
- Bias in favor of positive findings (journals, grant organizations)
- Overreliance on impact factors
- Overreliance on just reading abstracts
- Competitiveness between individuals, labs, countries, and even research councils

Look at CF for some ideas about how things can go well in terms of institutions, funding etc.

- Story of Trikafta (Vertex Pharmaceuticals), which helps all those with F508del (more than 80%)
- Vertex's first drug was ivacaftor/Kalydeco (approved 2012) which worked for the G551D mutation (a few percent). And another two combo drugs for various mutations: Orkambi 2015 and Symdeco 2018 all based on in vitro cell models. If 2 drugs could work better, why not 3? CFF gave money to Vertex (which bought Aurora). Note: not a 1:1 relationship between mutations and therapies. There are "theratypes"
- Focus on CFTR modulaters, correctors, potentiators (not on genes)
- Testing in vitro of cell culture systems has been sufficient for FDA approval for some rare mutations.
- https://www.statnews.com/2019/10/23/we-conquered-a-disease-how-vertex-delivered-a-transformative-medicine-for-cystic-fibrosis/
- NOTE: looks promising, but long term results not yet in

2. Social/Institutional/Communicative Challenges

"like being in a car that we don't know how to drive"

Vittorio Bellotti, Feb 26, 2021

Need for a new, realistic ethos of science that acknowledges and addresses its non-Mertonian features.

Thank you!