SYGNATURE DISCOVERY

Better trials demand better oncology drugs…

…but how do we deliver them?

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Enabling Success

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What makes a good drug?

- Potency
- Selectivity
- Pharmacokinetics
- Pharmacodynamics
- Safety
- Stability
- Novelty
- Ease of synthesis
- Formulation
- Commercially viable

What do patients say makes good drug?

- Cure vs control
- Secondary disease limitation / eradication
- Safer
- More effective
- Fewer side effects
- Better Quality of Life
- Convenience

Delivering better drugs

- CNS oncology
- Better combination therapies
- Better delivery systems
- Alternate drug targets

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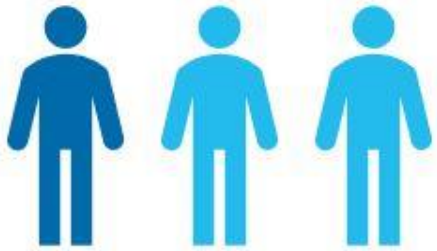
CNS oncology



1 of 3 people who die of cancer…

…have evidence of brain metastasis at autopsy

- Most of the recent oncology drugs are poorly CNS-penetrant
- Significant need in, *e.g.* breast cancer, lung cancer…

- Demands we think more about brain-penetrant compounds in drug discovery
- *How can clinical insight help us understand the most significant areas of unmet need?*

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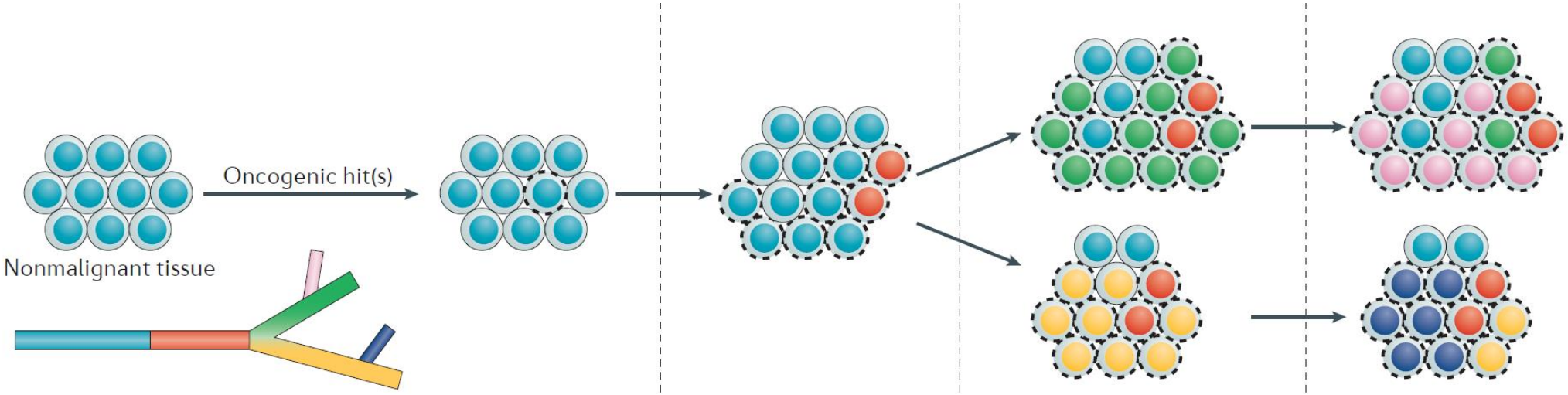
Combination therapeutics



- Targeted therapeutics select for specific cancer cell clones
- Frequently lead to outgrowth of resistant subclones that repopulate to cause relapse

Nature Reviews Clinical Oncology, 2018, p81

Overcoming resistance through clonal selection

- Combination of agents inhibiting multiple pathways can deliver prolonged clinical response
  - *e.g.* dabrafenib / trametinib in melanoma

- But:
  - Cancer drugs have always been designed to push the limits of tolerability as single agents to deliver maximum therapeutic benefit
  - Dose-limiting toxicities often lead to dose reductions, to potentially sub-therapeutic levels

- **Demands better tolerated agents where side effect profiles allow co-dosing at biologically effective doses**

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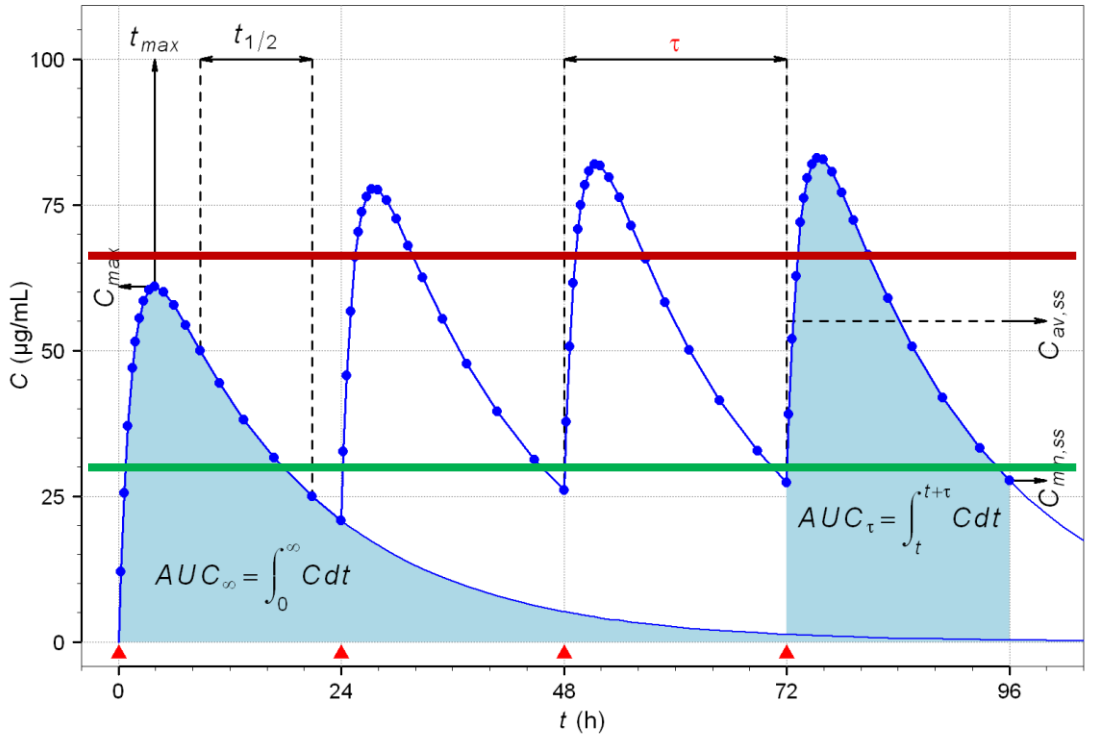
Drug delivery

- Drug exposure in humans can be unpredictable
  - Fine line between effective concentration and side effects…



Maximum TD

Minimum BED

Drug delivery

- Can we develop better delivery techniques for more linear drug delivery?
- Efficacious, sustained, consistent and predicable exposure?
  - *e.g.* bicalutamde (Casodex) implants
  - Trans-dermal patches
  - Alternate medical devices?
- May deliver more uniform dosing, above BED but below MTD for better tolerability?
- Demands engagement with formulation and delivery expertise

Delivering better drugs

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Better drug targets?

- Are there more effective ways of killing cancer cells?
- How do we find better points of intervention?

The PD-(L)1 syndrome

- > 2,250 PD(L)-1 trials ongoing, requiring over 400,000 patients
- Does this deliver any further, *significant*, patient benefit?

- Or is this approach unsustainable, for only minor, incremental, reward?

Re-thinking drug target identification

LETTERS
https://doi.org/10.1038/s41591-019-0380-z
nature medicine

Utility of ctDNA to support patient selection for early phase clinical trials: the TARGET study

Dominic G. Rothwell[1], Mahmood Ayub[1], Natalie Cook[2,3], Fiona Thistlethwaite[2,3], Louise Carter[2,3], Emma Dean[2,3], Nigel Smith[1], Shaun Villa[2,3], Joanne Dransfield[2], Alexandra Clipson[1], Daniel White[1], Kamrun Nessa[1], Saba Ferdous[1], Matthew Howell[1], Avinash Gupta[2], Bedirhan Kilerci[1], Sumitra Mohan[1], Kris Frese[1], Sakshi Gulati[1], Crispin Miller[1], Allan Jordan[4], Helen Eaton[5], Nicholas Hickson[5], Ciara O'Brien[2], Donna Graham[2], Claire Kelly[2], Sreeja Aruketty[2], Robert Metcalf[2], Jaseela Chiramel[2], Nadina Tinsley[2], Alexander J. Vickers[2], Roopa Kurup[2], Hannah Frost[2], Julie Stevenson[1], Siobhan Southam[1], Dónal Landers[1,6], Andrew Wallace[5], Richard Marais[7], Andrew M. Hughes[3,9], Ged Brady[1,9], Caroline Dive[1,8,9*] and Matthew G. Krebs[2,3,9*]

Molecular profiling…

- Patient stratification allows some patients access to hitherto unidentified options
- Frustratingly, more often than not, the outcome is "*nil actionable*"
- Are these a source of unexplored therapeutic opportunities?
- **How, as a community, do we share, explore and resolve these for patient benefit?**
  - *How many stratification trials with molecular profiling proactively include drug hunters?*
- *Can we convert the "Nil actionables" to the "New actionables"?*

In summary:

- To really make a difference to patient outcomes, I believe that the drug discovery community needs to get significantly better at:
  - Understanding the needs and requirements of patients
  - Understanding the clinical landscape
  - Developing more efficacious therapies for ^{n}th line patients
    - CNS disease
    - Tumour heterogeneity
    - Entrenched resistance, e.g. 2^{ndry} TNBC
  - Developing alternate modalities for formulation and drug delivery

But…

- Drug discovery cannot do this in isolation
- Very few drug hunters understand the clinical landscape well enough to implement these changes most effectively
- If we are to succeed, **we need the help of the clinical community**
  - To change our mindsets, to change our approaches, to enrich our understanding of disease and to truly make a difference to our patients.

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Thank you!

https://www.sygnaturediscovery.com/news-and-events/rethinking-drug-discovery/

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