Patient-Centered Reverse Translation

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Key Take Home Message

- Research starts with and returns to the patient
- Powerful trend in research and medicine focusing on patient-centricity
- Precision medicine approaches driven by reverse translation drives companion diagnostics
• Reverse. [adjective] Going in or turned towards the direction opposite to that previously stated.

• Translation. [noun] The process of translating words or text from one language into another.
Therapy & Tools

Patient

Mechanism

Target

Wagner CPT 2018;103:168-170
Forward Translation

- Application or translation of laboratory research to clinical experiments or patients
- Bench-to-bedside
Bench-to-bedside approach is limiting

- The most obvious limitations are in target discovery and the frequent route reversals necessary for drug discovery and development
- Targets do not emerge from a vacuum, and that is where a patient-centered reverse translation approach is particularly critical
Reverse Translation

- Application or translation of clinical, patient-centered data to laboratory research
- Bedside-to-bench
Reverse translation (A & B)

- Reverse translation activities aim to explain disease and patient biology through an integrative, cross-functional approach linking “omic” data derived from a deep characterization of patients with their health phenotype data.
- The goal is to generate actionable hypotheses about disease mechanisms and drug response supporting validation of existing targets, identifying new targets and disease mechanisms/indications and driving precision medicine strategies.
- Data for reverse translation can be derived from exploratory characterization of patients in clinical trials, non-interventional human studies or through access to well characterized patient databases/tissue repositories, including public-profit consortia efforts.
- Precision medicine strategies may ultimately become companion diagnostics.
Reverse translation (E)

• Forward translation does not formally account for the critical reverse steps
• Learnings from patients that are reflected back to drug discovery and development tools (e.g., biomarkers, animals models, or modeling and simulation approaches, including quantitative disease models)
• Refinements of a therapeutics (e.g., pharmacokinetically unacceptable profiles leading to different desired molecular or metabolic properties)
1. Experiment of Nature
PCSK9 mutations associated with remarkably low cholesterol and reduced incidence of coronary artery disease

2. Understanding LDL Mechanism
PCSK9 null mice confirmed low cholesterol and PCSK9 binding LDL receptors linked with control of LDL cholesterol levels

3. Inhibition of PCSK9
Discovery of antibody inhibitors of PCSK9 resulted in forward translation of therapeutics that reduced degradation of LDL receptors and lowering cholesterol levels

4. IMPLEMENTATION: A NEW APPROACH
Monoclonal antibodies, alirocumab and evolocumab, were approved 12 years after the initial bedside observations, and have been shown to dramatically reduce LDL cholesterol in patients with hypercholesterolemia
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MC4R Mechanism of Action

Agonism of MC4R proposed to ↓ food intake and weight

Leptin

MC4R

Fat mass ↓

Leptin

Lipolysis ?

RQ ↓
Insulin sensitivity (↑)
Glucose uptake (↑)

energy use ↑

Glucose production (↓)

Insulin release (↓)

Food intake ↓
Strong target validation, particularly genetic evidence

- Humans with mutations in MC4R
  - have obesity, hyperphagia (binge-eating), hyperinsulinemia
  - homozygotes worse than heterozygotes
  - similar syndrome in POMC-deficient humans

- MC4R knockout mice
  - similar phenotype as humans

- Animal pharmacology in rodents
  - MC4R antagonists increase food intake and body weight
  - MC4R agonists decrease food intake and body weight
  - effects in wild-type but not MC4R-knockout mice
Single 500-mg MK-0493 Dose Had Marginal Effects on 24-hr Food Intake

24-hr intake:
Sibutramine: ~18% ↓
500 mg MK-493: ~ 7% ↓

Krishna R et al CPT
2009 Dec;86(6):659-66
Hint of Efficacy in POC Study in Obese Patients
Suggested Higher Exposures May Be Necessary

- Mean Change in Body Weight (kg)
  - Placebo (N=64)
  - L-000222628 200 mg (N=65)
  - L-000222628 400 mg (N=61)

- Significance from placebo established at Week 2 with N=80 per group

- Efficacy of 200 mg diminishes after 4 weeks; 400 mg diminishes after 8 weeks (p=0.154 at week 12)

- Rashes appear in 400 mg group 7-21 days on treatment

- 400 mg
  - AUC ~ 8.9 µM.hr
  - C_{24hr} ~ 108 nM

Krishna R et al CPT 2009;86:659-66
Repeat POC Study with MK-0493, Done at MTD, Indicated Weight Loss was Not Statistically Significant

Probability >2.1 kg is ~11%
Targeting Upstream MC4 Pathway Defects Rare Diseases

MC4 Pathway

Rhythm Focus

Upstream Downstream

Decreased Appetite
Decreased Weight

MC4R
Setmelanotide

LEPTIN SIGNAL

Leptin Receptor Deficiency
POMC Deficiency
POMC Hetz / POMC Epigenetic Deficiency

Bardet-Biedl & Alström Syndromes

POMC Neurons

PCSK

MSH

MC4R

MC4 Neurons


Clinical Chemistry 2005; 51: 1358.
POMC Deficiency Obesity Phase 2 Study

Kühnen, M.D., Karine Clément, M.D., Susanna Wiegand, M.D., Oliver Eisenstein, M.D., Keith Gottesdiener, M.D., Lea L. Martini, M.D., Knut Mai, Ulrike Blume-Peytavi, M.D., Annette Grüters, M.D., and Heiko Krude,
Vision for translational medicine

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