VII CORSO del GRUPPO ITALIANO DI EMATOPATOLOGIA

La DIAGNOSTICA EMATOPATOLOGICA nell'ERA della MEDICINA di PRECISIONE

Il valore del "drug repourposing"

From a single clinical case to a scalable drug repurposing strategy

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Bologna, Aula Prodi | 11-12 maggio 2026

Disclosures of Name Surname

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other

Clinical Case:

- Male 23 yo, MD student
- Idiopathic multicentric Castleman disease (iMCD)
- Recurrent cytokine storm and multiorgan failure
- No approved therapies available at diagnosis
- 7 lines of chemotherapy "off label" which led to temporary remission
- 5° relapse…something changed..

- The patient himself asked for genetic testing aiming to use an "off label" repourposed drug….
- Upregulated mTOR signaling
- Pathway-driven hypothesis
- Repurposing of Sirolimus

Follow up…. Durable remission >10 years

David Fajgenbaum

From One Patient to a General Question

- How many diseases lack therapies despite available drugs?
- Main limitation: fragmented and not fully shared biomedical knowledge
- Castleman Disease repourposed treatment as a model, not an exception

The Treatment Gap

- ~18,000 recognized diseases worldwide
- ~4,000 with approved drug therapies

>75% without codified treatments
>300 million affected globally

80% of FDA-approved drugs are off-patent and unprofitable, so companies are not incentivized to invest in further research to find additional uses for these drugs.

No one has ever taken care and responsibility of this "gray zone"

Birth of Every Cure

- Founded in 2022 as a **non-profit** platform
- Mission: evaluate all drugs across all diseases

Disease-agnostic approach

- Focus on rare and immune-mediated disorders
- Focus on *generic / off-patent* compounds

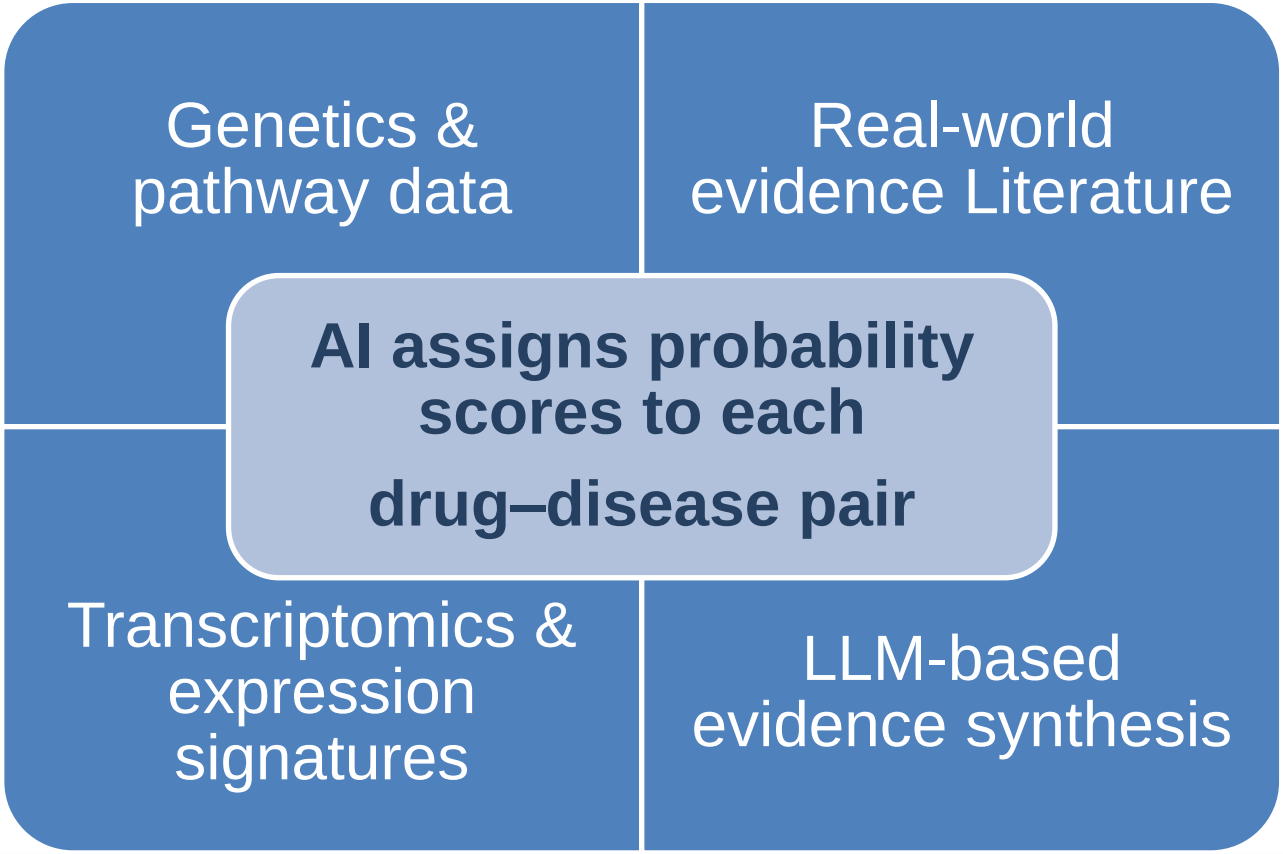
All Drugs × All Diseases

- ~18,000 recognized diseases worldwide
- ~4,000 with approved drugs

~75 million drug–disease pairs evaluated simultaneously

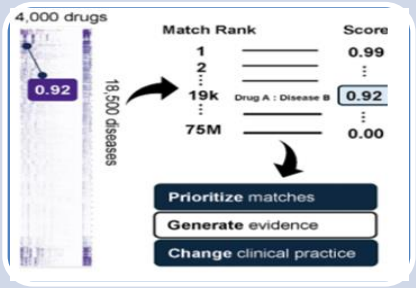
Analysis time ~17 hours

Computational Pharmacophenomics



Meaning of "High Ranking in the algorithm"

Ranking prioritizes hypotheses,



Human-in-the-Loop Review

Pathologists, clinicians, and biologists assess

1.biological plausibility

2.clinical feasibility

Filters out false positives

retrains the model continuously

Development Paths

Internal classification by evidence and impact

Validation strategy selected case by case

Possible Development Paths

Unsung Hero

This opportunity has sufficient clinical evidence of efficacy, but further action is needed to close gaps in patient access

Clinical Gem

This opportunity needs more clinical evidence (e.g., a clinical trial) in order to progress to patients

Frontier Explorer

This opportunity needs more laboratory studies (e.g., testing on cells) in order to progress to clinical studies

Salvage setting	Biological + clinical
Rare disease	Case series / observational
Advanced programs	Prospective studies
Broad adoption	Formal clinical trials

- Rational off-label use in salvage settings
- Observational studies and case series
- Preclinical validation
- Formal clinical trials when signal is strong

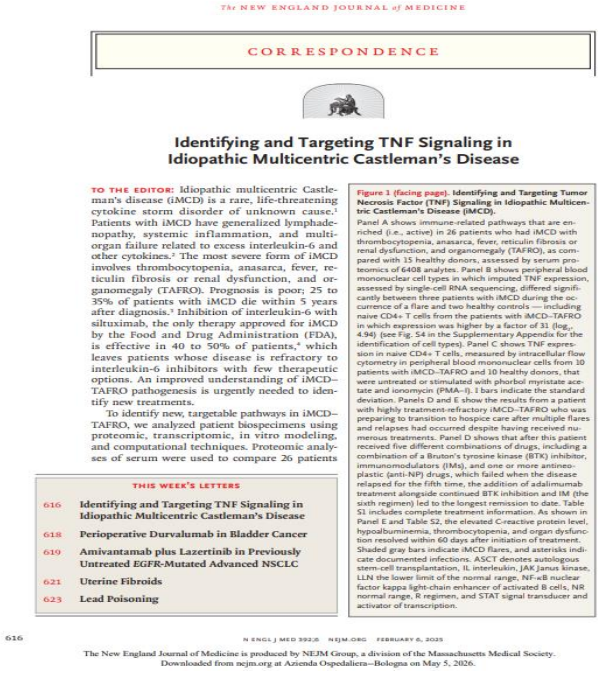
First Patient Treated via Algorithm

- iMCD patient refractory to all therapies
- Adalimumab identified as top-ranked candidate
- Rapid organ recovery and remission

The NEW ENGLAND JOURNAL of MEDICINE

Unsung Hero

This opportunity has sufficient clinical evidence of efficacy, but further action is needed to close gaps in patient access



The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

Identifying and Targeting TNF Signaling in Idiopathic Multicentric Castleman's Disease

TO THE EDITOR: Idiopathic multicentric Castleman's disease (iMCD) is a rare, life-threatening cytokine storm disorder of unknown cause.[1] Patients with iMCD have generalized lymphadenopathy, systemic inflammation, and multiorgan failure related to excess interleukin-6 and other cytokines.[2] The most severe form of iMCD involves thrombocytopenia, anasarca, fever, reticulin fibrosis or renal dysfunction, and organomegaly (TAFRO). Prognosis is poor; 25 to 35% of patients with iMCD die within 5 years after diagnosis.[3] Inhibition of interleukin-6 with siltuximab, the only therapy approved for iMCD by the Food and Drug Administration (FDA), is effective in 40 to 50% of patients,[4] which leaves patients whose disease is refractory to interleukin-6 inhibitors with few therapeutic options. An improved understanding of iMCD–TAFRO pathogenesis is urgently needed to identify new treatments.

To identify new, targetable pathways in iMCD–TAFRO, we analyzed patient biospecimens using proteomic, transcriptomic, in vitro modeling, and computational techniques. Proteomic analyses of serum were used to compare 26 patients

Figure 1 (facing page). Identifying and Targeting Tumor Necrosis Factor (TNF) Signaling in Idiopathic Multicentric Castleman's Disease (iMCD).

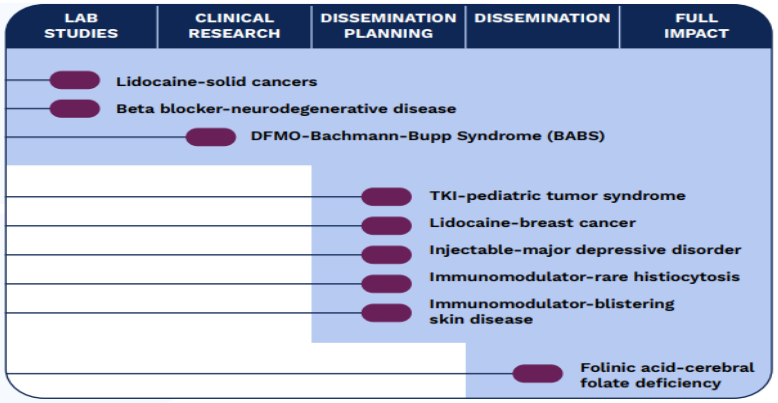
Panel A shows immune-related pathways that are enriched (i.e., active) in 26 patients who had iMCD with thrombocytopenia, anasarca, fever, reticulin fibrosis or renal dysfunction, and organomegaly (TAFRO), as compared with 15 healthy donors, assessed by serum proteomics of 6408 analytes. Panel B shows peripheral blood mononuclear cell types in which imputed TNF expression, assessed by single-cell RNA sequencing, differed significantly between three patients with iMCD during the occurrence of a flare and two healthy controls — including naive CD4+ T cells from the patients with iMCD–TAFRO in which expression was higher by a factor of 31 ($\log_2$ 4.94) (see Fig. S4 in the Supplementary Appendix for the identification of cell types). Panel C shows TNF expression in naive CD4+ T cells, measured by intracellular flow cytometry in peripheral blood mononuclear cells from 10 patients with iMCD–TAFRO and 10 healthy donors, that were untreated or stimulated with phorbol myristate acetate and ionomycin (PMA–I). ‡ bars indicate the standard deviation. Panels D and E show the results from a patient with highly treatment-refractory iMCD–TAFRO who was preparing to transition to hospice care after multiple flares and relapses had occurred despite having received numerous treatments. Panel D shows that after this patient received five different combinations of drugs, including a combination of a Bruton's tyrosine kinase (BTK) inhibitor, immunomodulators (IMs), and one or more antineoplastic (anti-NP) drugs, which failed when the disease relapsed for the fifth time, the addition of adalimumab treatment alongside continued BTK inhibition and IM (the sixth regimen) led to the longest remission to date. Table S1 includes complete treatment information. As shown in Panel E and Table S2, the elevated C-reactive protein level, hypoalbuminemia, thrombocytopenia, and organ dysfunction resolved within 60 days after initiation of treatment. Shaded gray bars indicate iMCD flares, and asterisks indicate documented infections. ASCT denotes autologous stem-cell transplantation, IL interleukin, JAK Janus kinase, LLN the lower limit of the normal range, NF-κB nuclear factor kappa light-chain enhancer of activated B cells, NR normal range, R regimen, and STAT signal transducer and activator of transcription.

THIS WEEK'S LETTERS

2025

Other Studies Generated

- Rosai–Dorfman disease: lenalidomide + dexamethasone
- Folate receptor alpha non verbal autism: leucovorin
- Repurposed **sirolimus-like approaches** in inflammatory diseases
- Lidocaine in solid tumors



What This Means for Rare Diseases

- Faster hypothesis generation
- Lower cost entry to clinical validation
- Democratization of treatment access
- Shift from serendipity to **systematic repurposing**

Unlock repurposed treatments for 15 to 25 diseases by 2030

Limitations

Rare disease by definition

- Limited patient samples
- Lack of real-world evidence (RWE)

Features of Academic research till now

- Limitations of preclinical models
- Data sharing
- Intellectual property concerns

What we still dont know

- Generalizability across disease
- Predictive accuracy at individual-patient level
- Best integration with molecular diagnostics
- Regulatory pathways for guideline adoption

Conclusions

- Castleman Disease repourposed treatment as a model, not an exception
- Every cure is an example of integration of AI models and biological interpretation

  Human feedback retrains the model continuously

- Translational value emerges when biology leads

Without biology, AI is just pattern recognition

Every Cure/ai platforms work when pathology/biology/clinical expertise drives the question.

Thank you

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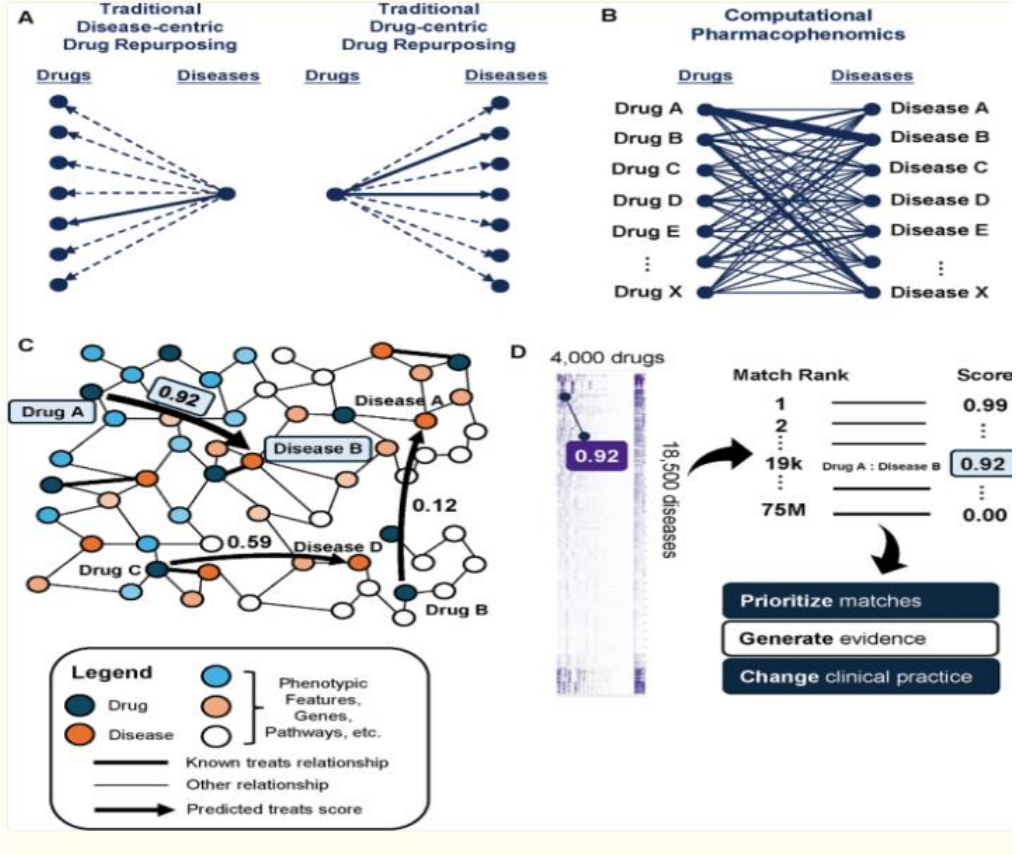
Elena Sabattini
Claudio Agostinelli
Carlo Alberto Sagramoso Sacchetti
Milena Piccioli
Anna Gazzola
Claudia Mannu
Gian Paolo da Pozzo
Federica Sandri
Debora Muscara
Silvia Pedrini
Thomas Gambarini
Cristina Grassigli
Francesca Conti
Daniela di Dio
Barbara Fattorini
Simona Righi
Maura Rossi

Sorbonne Université, Paris
Francesca Venturi

- http:// //everycure.org
- http://txgnn.org/
- http://ui.transltr.io/



Fajgenbaum DC, Lancet Haematol. 2025 Feb;12(2):e94-e96. doi: 10.1016/S2352-3026(24)00278-3.

regulatory

- **Drug repurposing does not bypass regulatory frameworks**
- **Off-label use remains physician responsibility**
- **Evidence generation pathways can be adaptive**
- **Regulatory approval required for guideline-level adoption**