Theo Zacharis

Greek Scientists Society

30 YEARS OF NRF2
CHARTING SUSTAINABLE PATHWAYS FOR THE FUTURE OF THE BENBEDPHAR ACTION

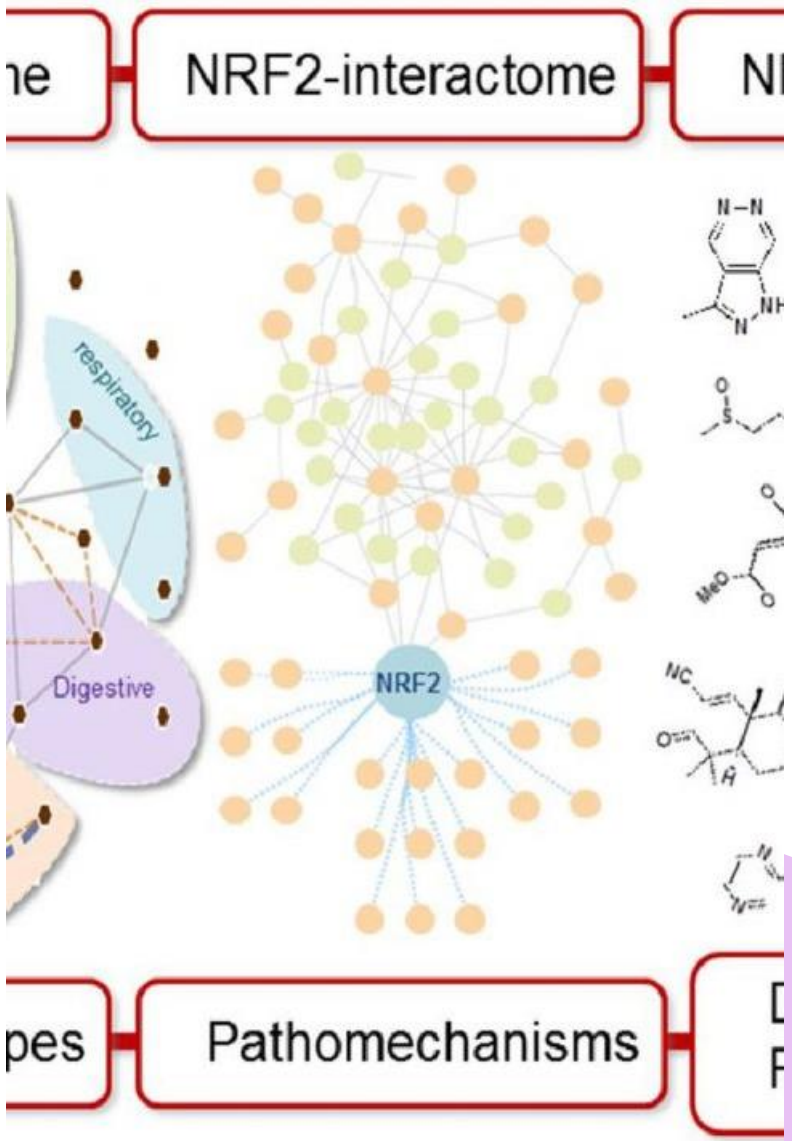
BenBedPhar

COST Action CA20121

Bench to Bedside transition for Pharmacological regulation of NRF2 in non communicable diseases

AGENDA

1. Introduction Historical Overview of NRF2
2. Translational Research From Discovery to Drug Development
3. Challenges in Therapeutic Applications
4. Current Landscape of NRF2-Related Clinical Trials and Patents
5. The Future of the NRF2 Community
6. BenBedPhar Sustainability Plans



GREEK SCIENTISTS SOCIETY

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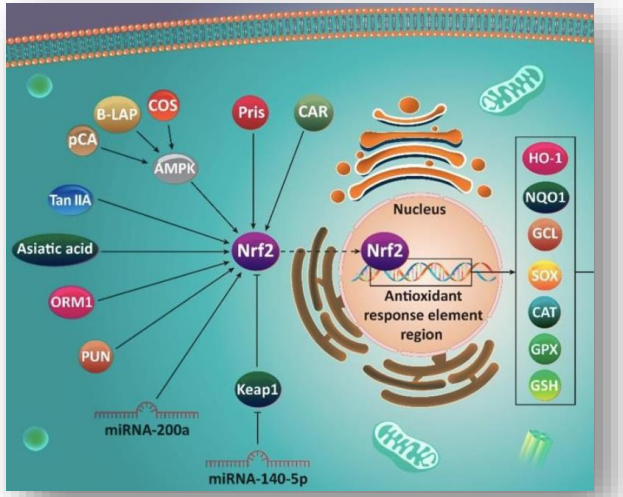
1. INTRODUCTION HISTORICAL OVERVIEW OF NRF2

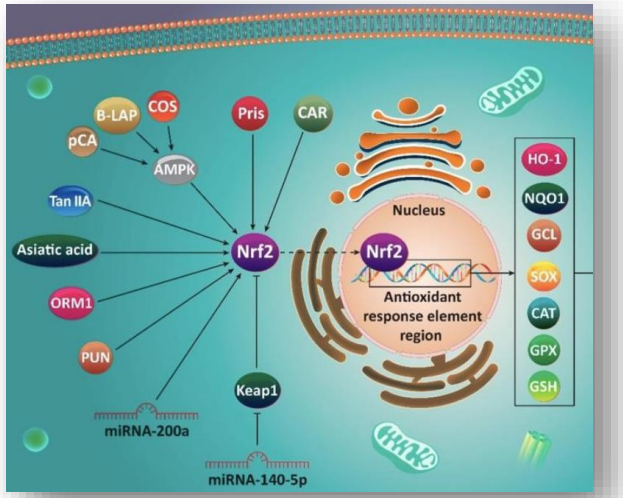
1. Discovery and Early Research (1994 - 2000)

- 1994 **NRF2 (Nuclear factor erythroid 2-related factor 2)** was discovered as a transcription factor that plays a critical role in regulating cellular defence mechanisms, particularly oxidative stress responses.
- Early studies revealed NRF2's ability to regulate the expression of detoxification and antioxidant genes, such as those encoding **glutathione** and **NAD(P)H** quinone dehydrogenase.
- NRF2 activation was found to be mediated by **KEAP1 (Kelch-like ECH-associated protein 1)**, which suppresses NRF2 under normal conditions and releases it during oxidative stress.



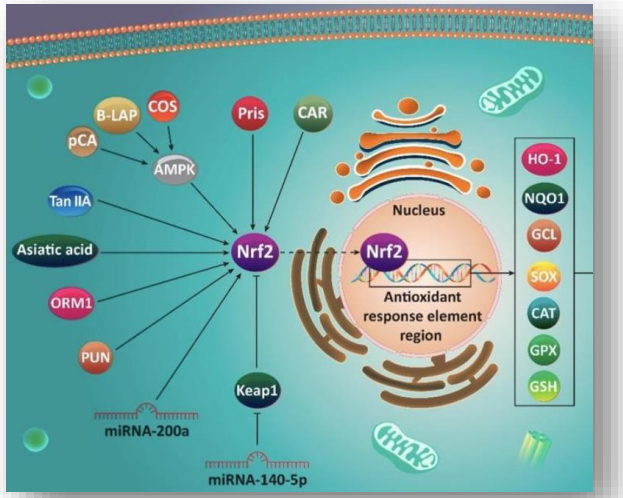
II. Link to Diseases and Pathways (2000 - 2010)

- Researchers began to link NRF2 activation to protection against various diseases, including **neurodegenerative diseases** (like Parkinson's and Alzheimer's), **cardiovascular diseases,** and **cancer**.
- The role of NRF2 as a "guardian of healthspan" emerged, recognising its ability to protect against environmental stresses and inflammatory processes.
- Preclinical models demonstrated the therapeutic potential of NRF2 activation in a wide range of diseases associated with **oxidative stress** and **inflammation**.



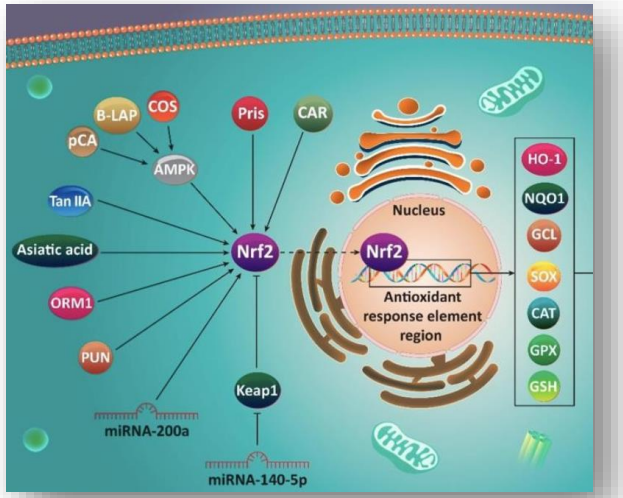
III. Development of Therapeutic NRF2 Activators (2010 - 2020)

- Several small molecules and dietary compounds were identified as NRF2 activators, with Sulforaphane from broccoli being one of the earliest known dietary activators.
- **Dimethyl fumarate (DMF)** became the first NRF2 activator to gain FDA approval in 2013, under the brand name **Tecfidera**, for the treatment of multiple sclerosis (**MS**). DMF activates NRF2, providing neuroprotection by reducing oxidative stress and inflammation.
- Research on **KEAP1 inhibitors** also gained momentum, exploring how these inhibitors could enhance NRF2 activation for therapeutic purposes.



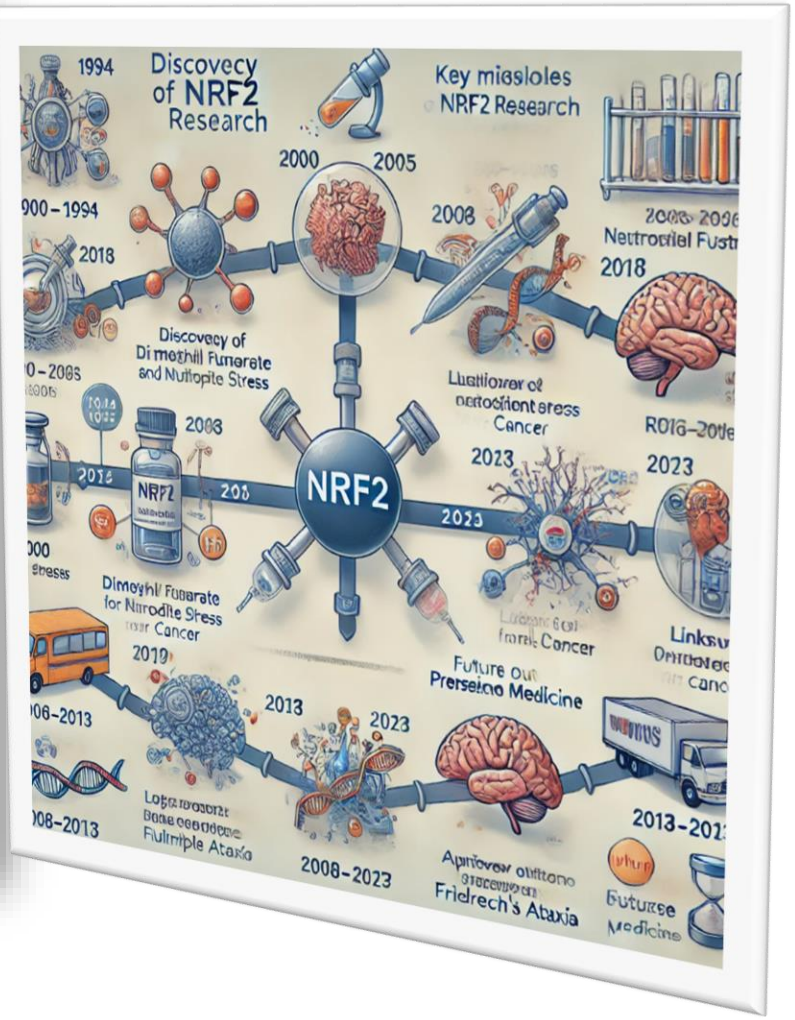
IV. Expanding Clinical Applications (2020 - Present)

- **Omaveloxolone**, another NRF2 activator, gained FDA approval in 2023 for treating **Friedreich's Ataxia**, a neurodegenerative disorder. This marked another significant step in NRF2-based therapies reaching clinical use.
- Ongoing research has explored NRF2's role in cancer, particularly focusing on how its **dual nature** can both protect cells from oxidative damage and, in some cases, promote cancer cell survival. This has made it a complex target in oncology.
- Clinical trials continue for NRF2 activators in conditions like chronic obstructive pulmonary disease (COPD), chronic kidney disease, and diabetes.



2. TRANSLATIONAL RESEARCH FROM DISCOVERY TO DRUG DEVELOPMENT

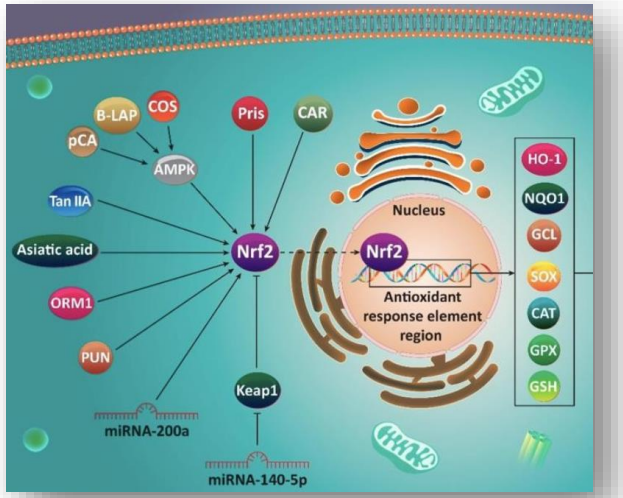
Disorder	Drug/Treatment	Therapeutic Approach
Neurodegenerative Diseases	Dimethyl Fumarate (Tecfidera)	NRF2 activator to reduce oxidative stress
Friedreich's Ataxia	Omaveloxolone	NRF2 activation through KEAP1 inhibition
Chronic Obstructive Pulmonary Disease (COPD)	Sulforaphane	Dietary NRF2 activator for antioxidant effects
Multiple Sclerosis	Monomethyl Fumarate (Bafiertam)	Similar to Tecfidera, activates NRF2 to reduce oxidative stress
Cancer	Bardoxolone Methyl	NRF2 pathway modulation for anti-inflammatory effects
Cardiovascular Diseases	N-Acetylcysteine (NAC)	Enhances NRF2-mediated antioxidant defence
Multiple Sclerosis	Fumarates (generic)	Broad-spectrum NRF2 activation for MS treatment



3. CHALLENGES IN THERAPEUTIC APPLICATIONS

V. Key Challenges and Future Directions

- **Selective Activation** One of the key challenges has been achieving selective NRF2 activation without off-target effects, especially since prolonged activation may lead to unwanted effects, such as tumour progression in some cancers.
- **Personalised Medicine** The future of NRF2 therapeutics may lie in personalised medicine, where therapies are tailored based on an individual's oxidative stress levels and genetic factors.
- **Beyond Small Molecules** Research is also expanding into RNA-based therapies, protein-protein interaction inhibitors, and more refined molecules to modulate the NRF2 pathway with greater specificity and fewer side effects.



3. CHALLENGES IN THERAPEUTIC APPLICATIONS

Several challenges exist in developing NRF2-based therapies for clinical applications, mainly related to the complexities of the NRF2 pathway and the balance between its protective and harmful effects.

1. Selective Activation of NRF2

Problem NRF2 activation is beneficial against oxidative stress and inflammation but prolonged or excessive activation can have adverse effects - cancer - where it might help cancer cells survive by protecting them from oxidative damage and chemotherapy

Approach Developing **selective modulators** of the NRF2 pathway that can target specific tissues or conditions without inducing unwanted long-term activation

2. Off-Target Effects

Problem Many NRF2 activators - early molecules - tend to be non-specific and can modify other proteins besides KEAP1 leading to off-target effects causing unpredictable results in clinical settings

Approach The development of more **selective compounds** or those that act specifically on KEAP1-NRF2 protein-protein interactions (PPIs) is an ongoing effort to reduce off-target effects

3. CHALLENGES IN THERAPEUTIC APPLICATIONS

Several challenges exist in developing NRF2-based therapies for clinical applications, mainly related to the complexities of the NRF2 pathway and the balance between its protective and harmful effects.

3. Dual Role in Cancer

Problem While NRF2 protects normal cells from oxidative stress, it can promote cancer cell survival by supporting their antioxidant defences, which helps them resist chemotherapy and radiation. This makes it difficult to balance NRF2 activation in cancer therapies

Approach Strategies to **inhibit NRF2 in cancers** where it is abnormally upregulated (such as non-small-cell lung cancer) while activating it in normal tissues are under investigation. Precision-targeted therapies are key to managing this dual role.

4. Bioavailability and Stability of Activators

Problem Many small-molecule NRF2 activators suffer from poor bioavailability, as they do not stay in the body long enough or fail to reach the target tissues effectively limiting their therapeutic potential

Approach Researchers are focusing on **improving the formulations** and **delivery methods** of NRF2 activators to ensure they reach their target tissues in effective concentrations.

3. CHALLENGES IN THERAPEUTIC APPLICATIONS

Several challenges exist in developing NRF2-based therapies for clinical applications, mainly related to the complexities of the NRF2 pathway and the balance between its protective and harmful effects.

5. Resistance Mechanisms

Problem Continuous activation of NRF2 can induce resistance mechanisms within the body, where feedback loops reduce the NRF2 activation effectiveness over time, e.g. proteins like BACH1 can inhibit NRF2's ability to sustain long-term responses to oxidative stress

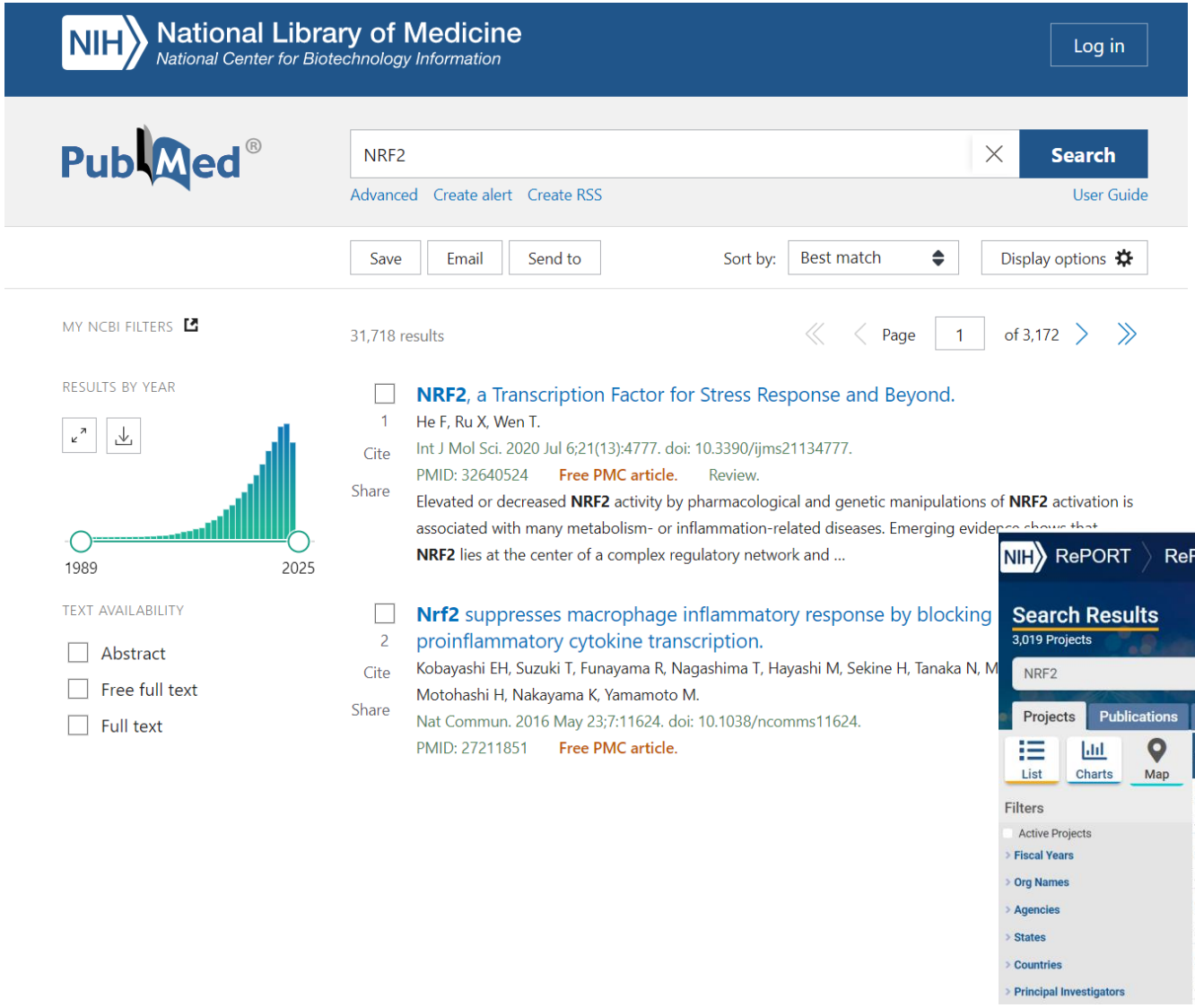
Approach Efforts are being made to overcome these **feedback inhibition mechanisms** and extend the duration and effectiveness of NRF2-based therapies

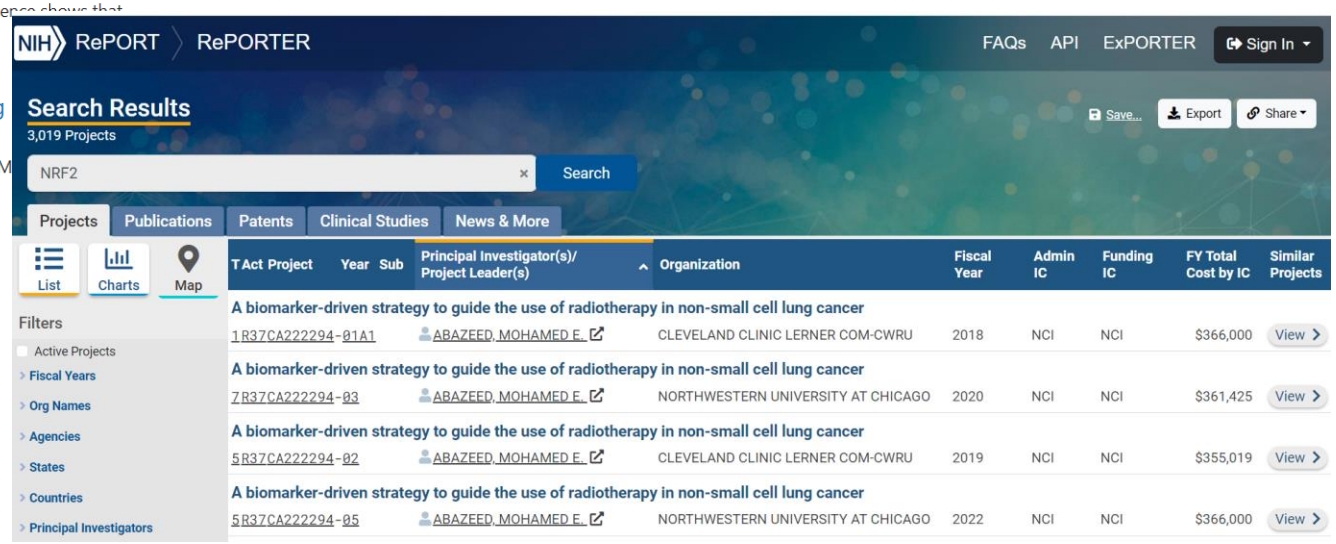
6. Patient-Specific Responses

Problem The benefits of NRF2 activation can vary significantly between patients, depending on their genetic background and the nature of their disease, e.g. patients with certain NFE2L2 mutations (the gene encoding NRF2) may not respond well to NRF2 activators

Approach **Personalised medicine** approaches, where NRF2 therapies are tailored to an individual's genetic profile and disease stage, are being explored to maximise therapeutic benefits

4. CURRENT LANDSCAPE OF NRF2-RELATED CLINICAL TRIALS AND PATENTS





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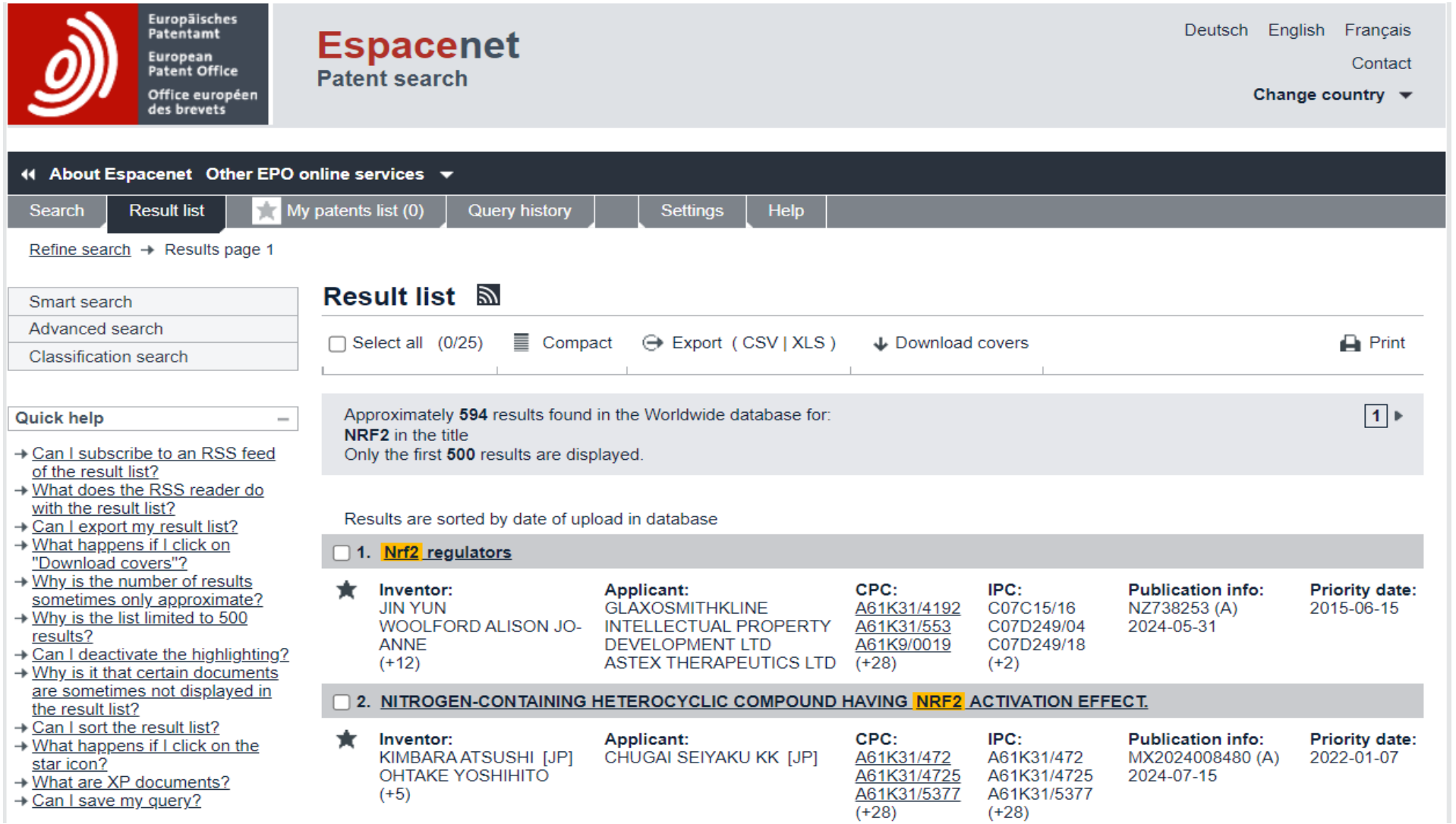

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Approximately **594** results found in the Worldwide database for:
NRF2 in the title
Only the first **500** results are displayed.

1

Results are sorted by date of upload in database

1. Nrf2 regulators

Inventor:	Applicant:	CPC:	IPC:	Publication info:	Priority date:
JIN YUN WOOLFORD ALISON JO-ANNE (+12)	GLAXOSMITHKLINE INTELLECTUAL PROPERTY DEVELOPMENT LTD ASTEX THERAPEUTICS LTD	A61K31/4192 A61K31/553 A61K9/0019 (+28)	C07C15/16 C07D249/04 C07D249/18 (+2)	NZ738253 (A) 2024-05-31	2015-06-15

2. NITROGEN-CONTAINING HETEROCYCLIC COMPOUND HAVING NRF2 ACTIVATION EFFECT.

Inventor:	Applicant:	CPC:	IPC:	Publication info:	Priority date:
KIMBARA ATSUSHI [JP] OHTAKE YOSHIHITO (+5)	CHUGAI SEIYAKU KK [JP]	A61K31/472 A61K31/4725 A61K31/5377 (+28)	A61K31/472 A61K31/4725 A61K31/5377 (+28)	MX2024008480 (A) 2024-07-15	2022-01-07

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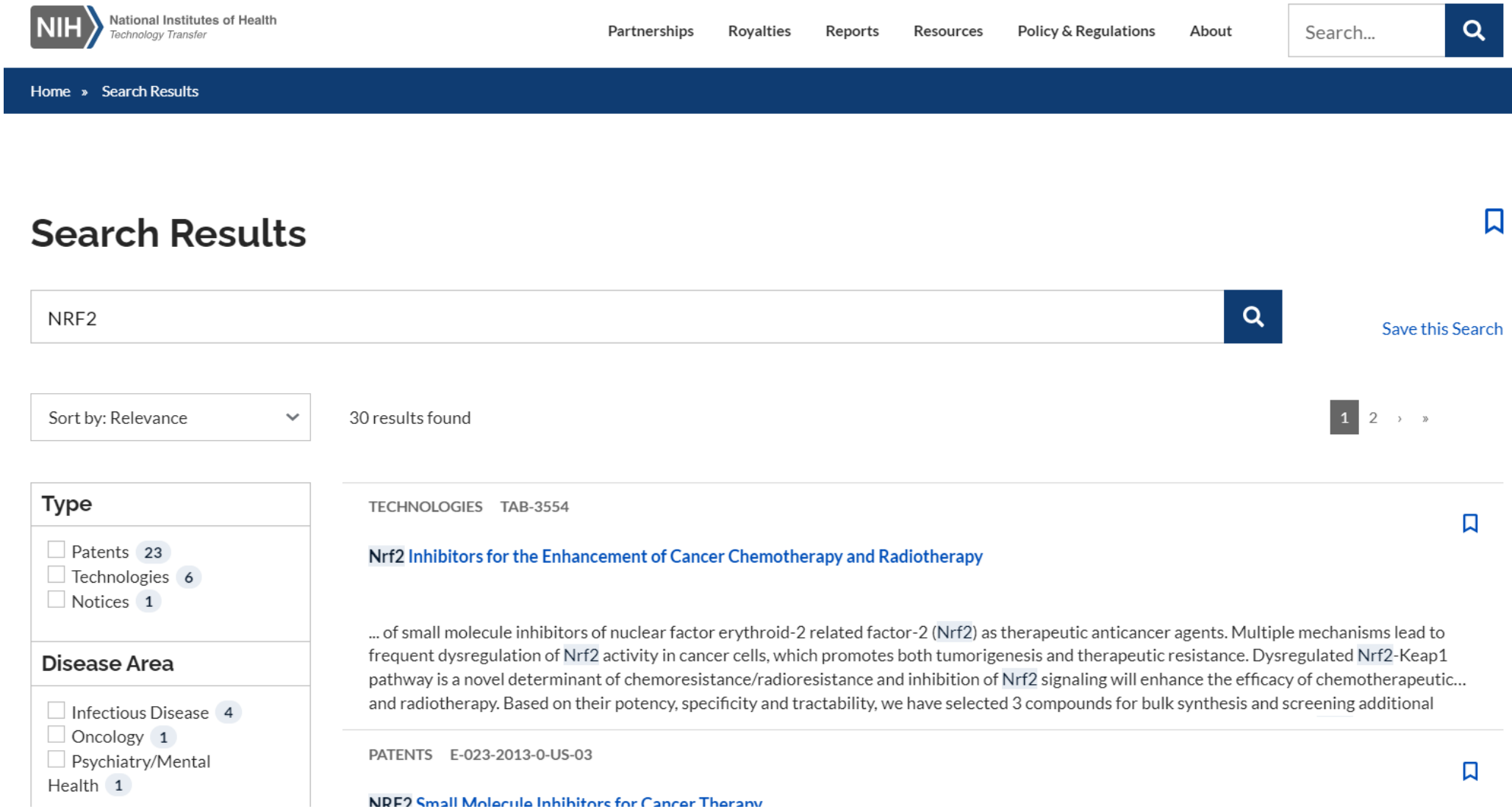

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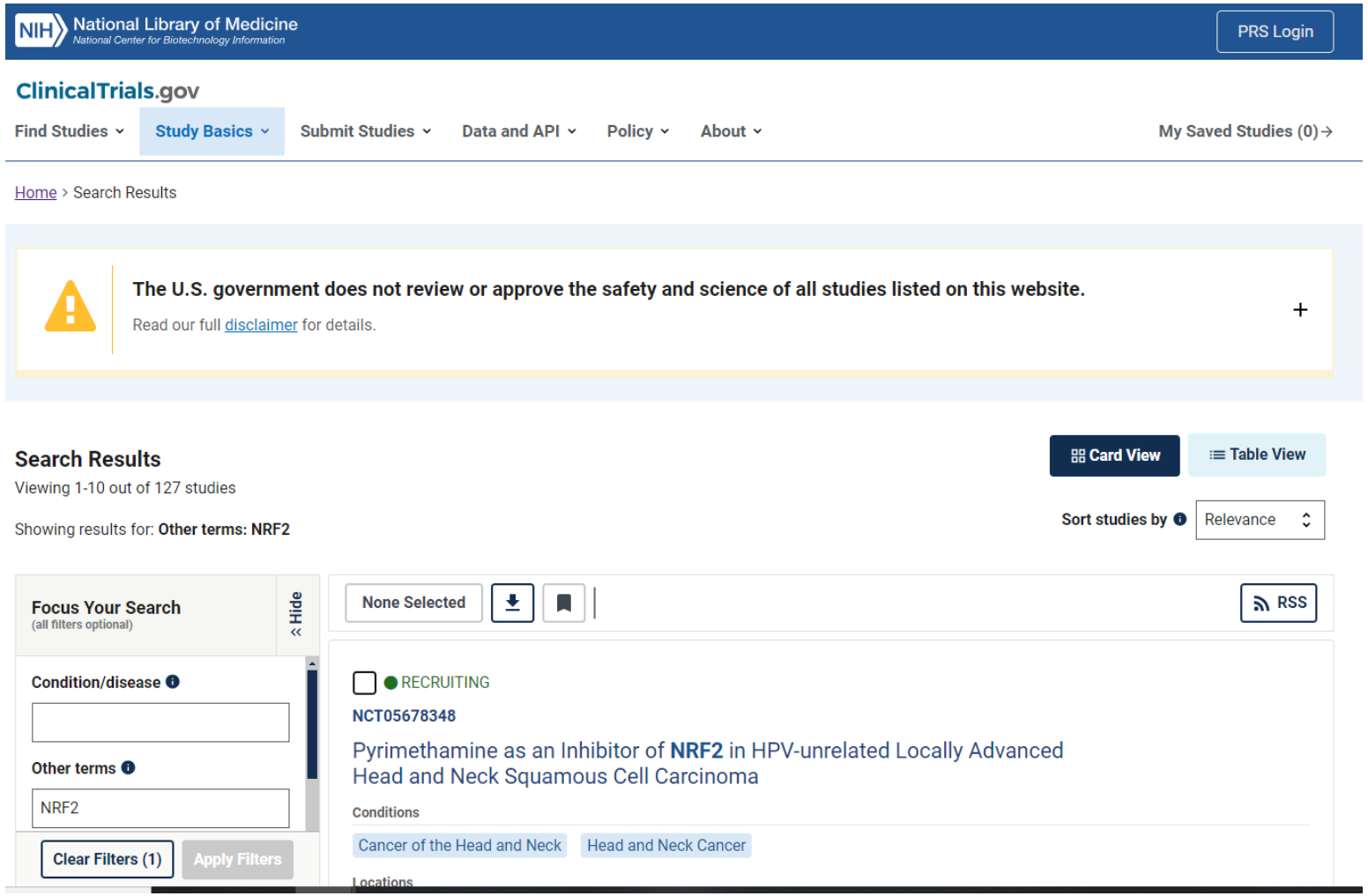

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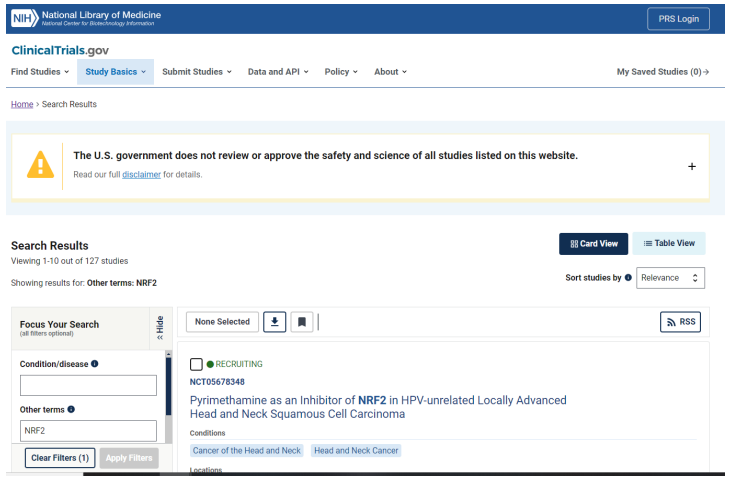

Year	Number of Clinical Studies	Key Focus
2000	5	Early studies on oxidative stress and immune modulation in chronic diseases.
2005	10	Trials on **Dimethyl Fumarate** for **Multiple Sclerosis** and psoriasis.
2010	18	Further trials on **Bardoxolone Methyl** for **chronic kidney disease**.
2013	26	**Dimethyl Fumarate (Tecfidera)** approved for **Multiple Sclerosis**; ongoing real-world studies.
2015	40	**Omaveloxolone** trials initiated for **Friedreich's Ataxia**.
2017	50	Expanded trials of **NRF2 activators** for broader applications in **diabetes** and **COPD**.
2020	75	Investigations into **Sulforaphane** for **autism**, and NRF2's role in **COVID-19** management.
2023	90+	Continued research on **NRF2** for neurodegenerative diseases and cancer therapies.

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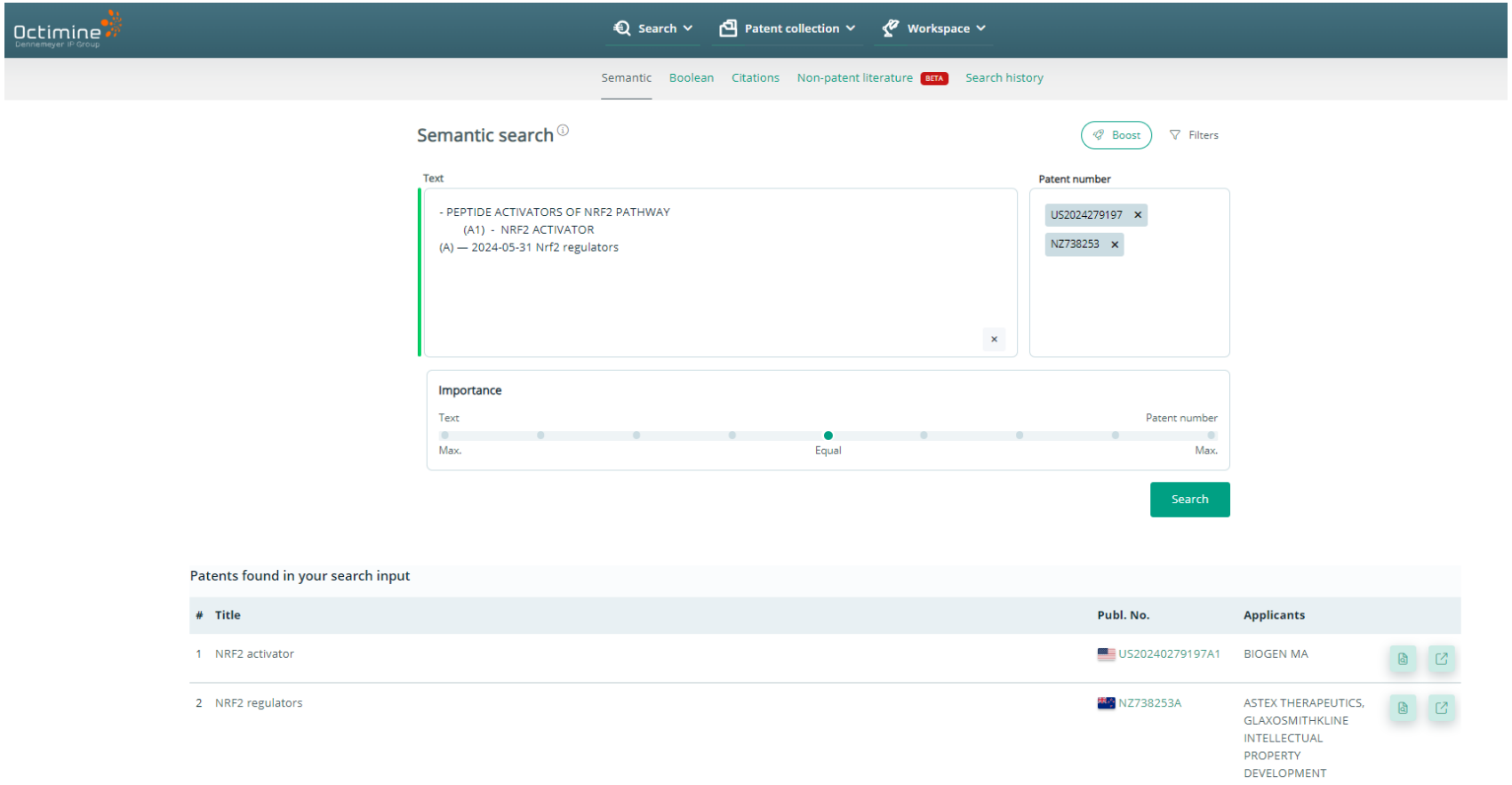

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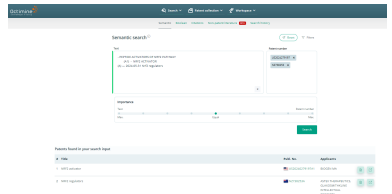
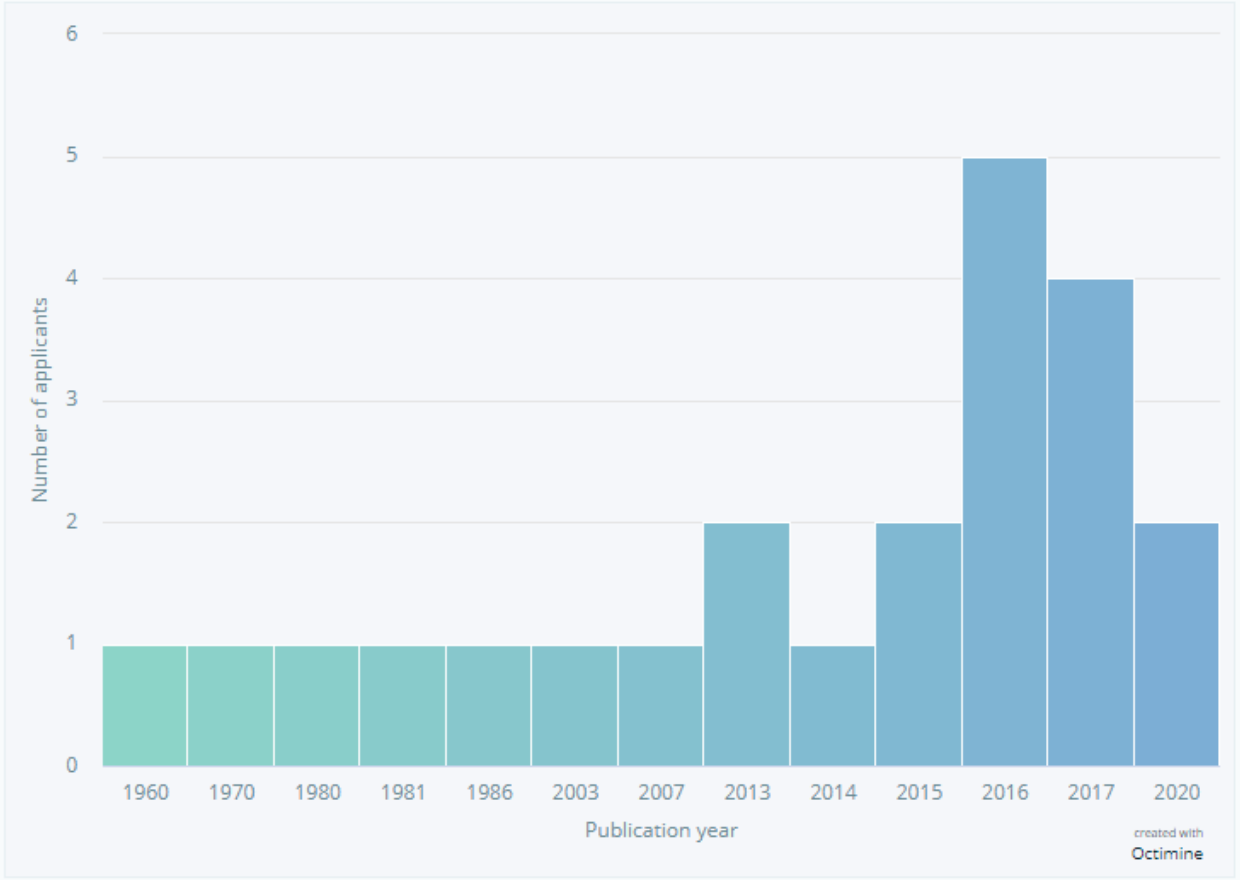
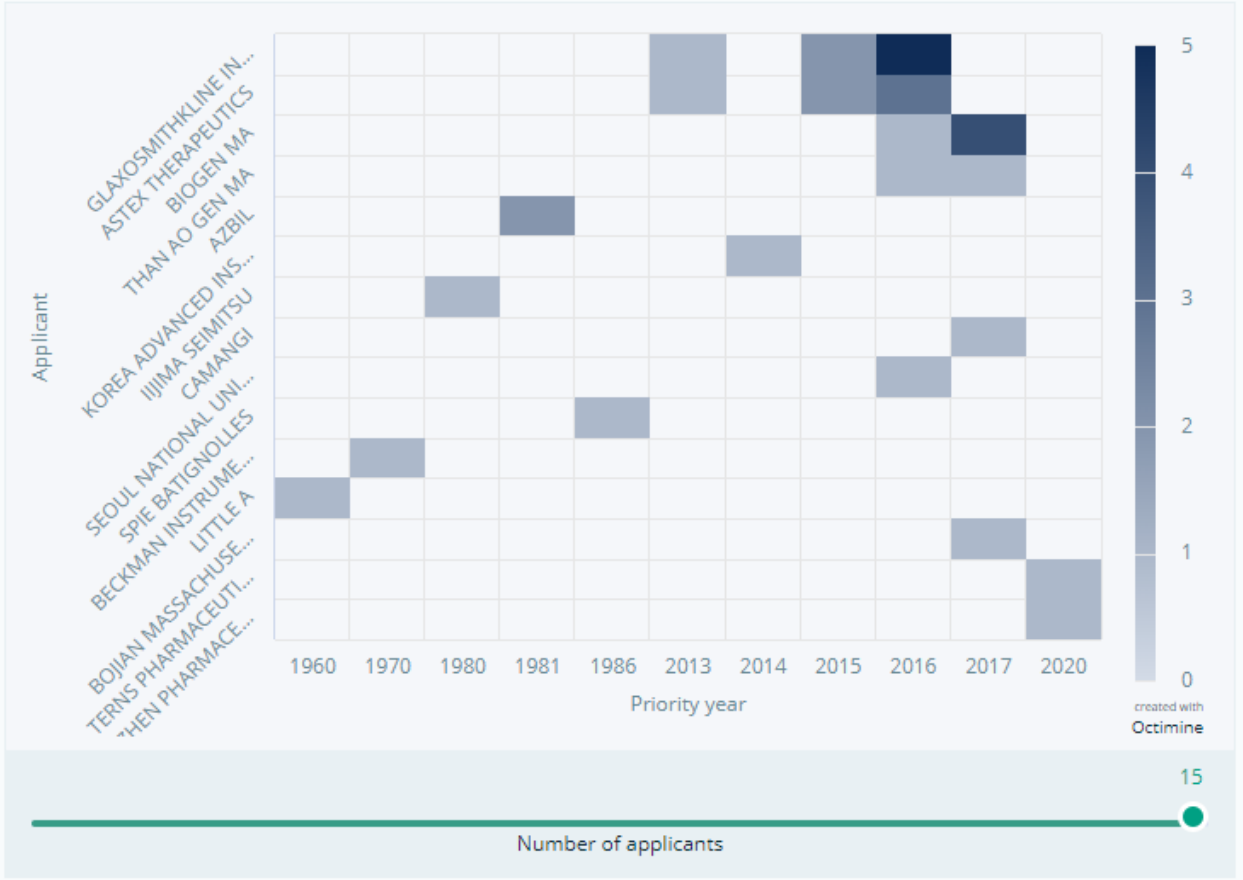


Number of applicants over time



Applicants over time



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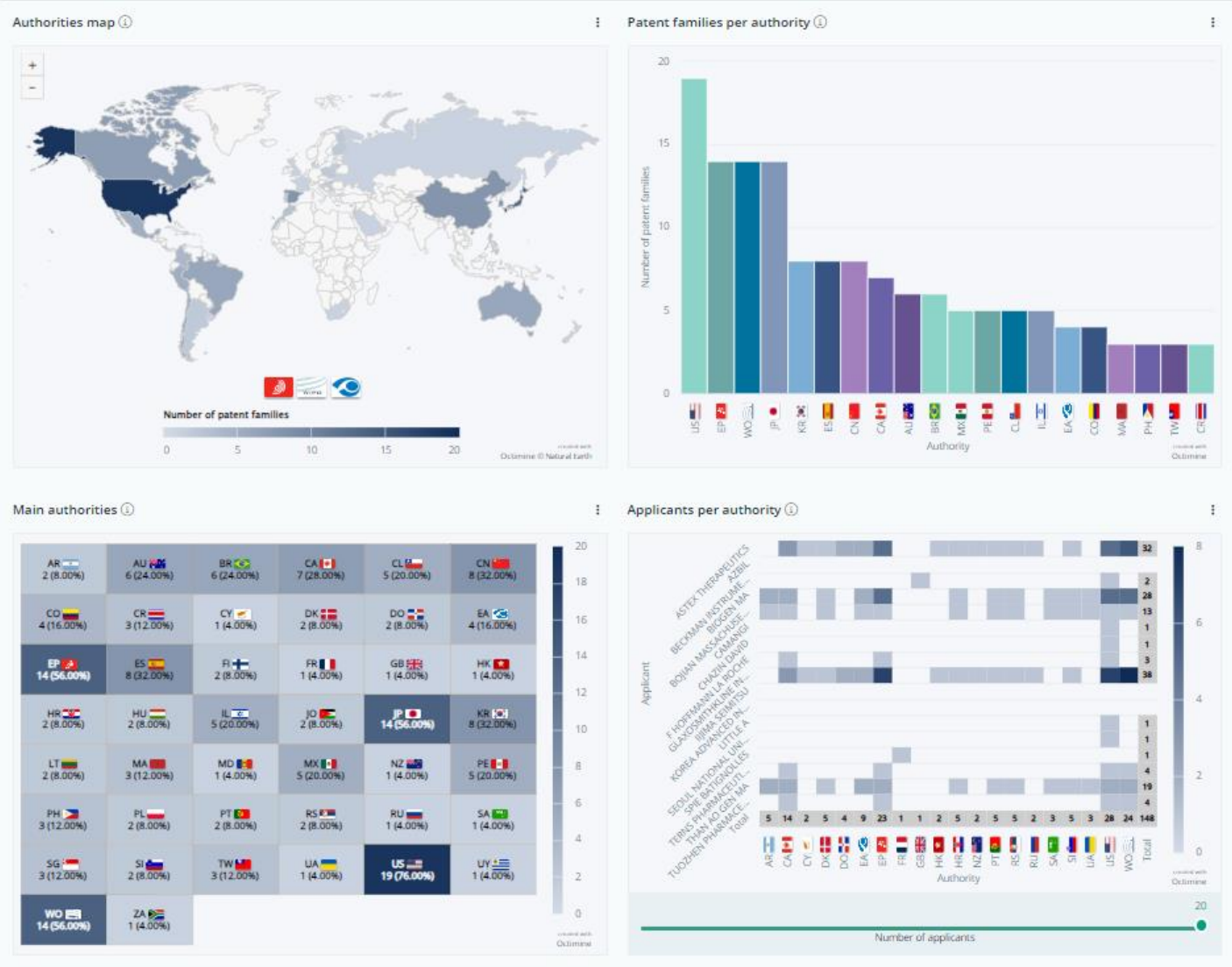

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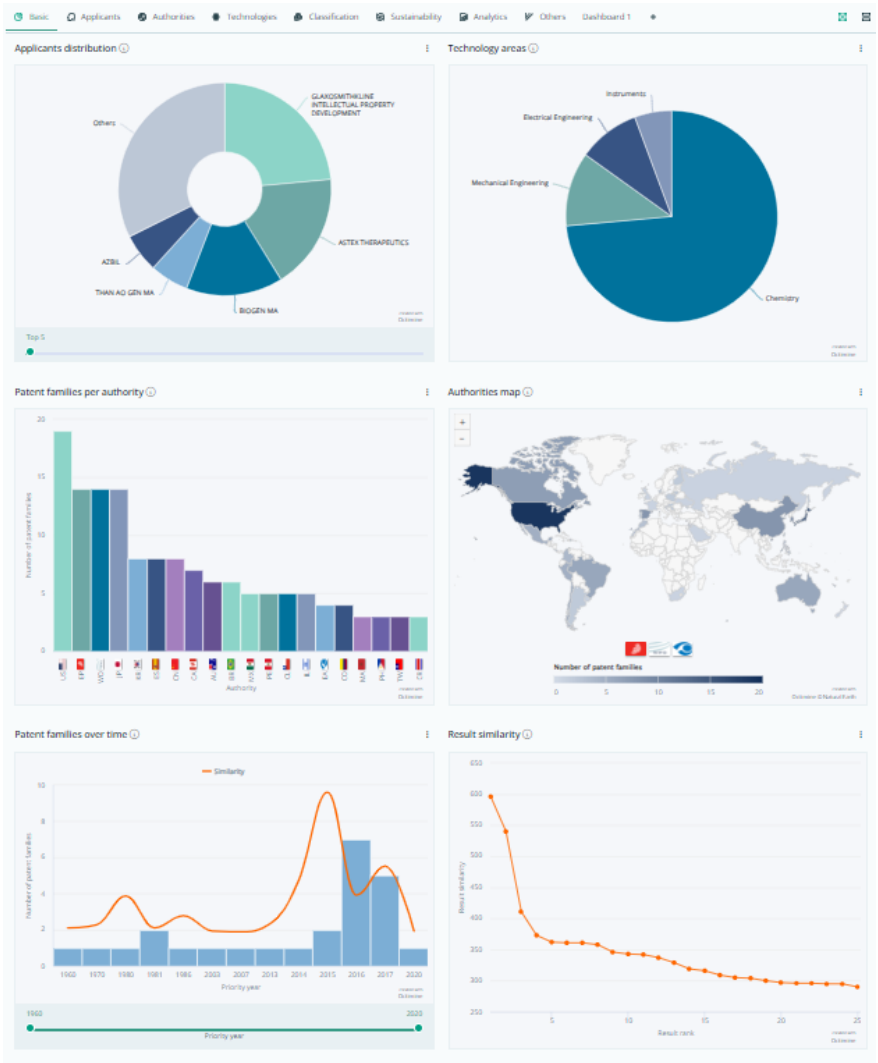

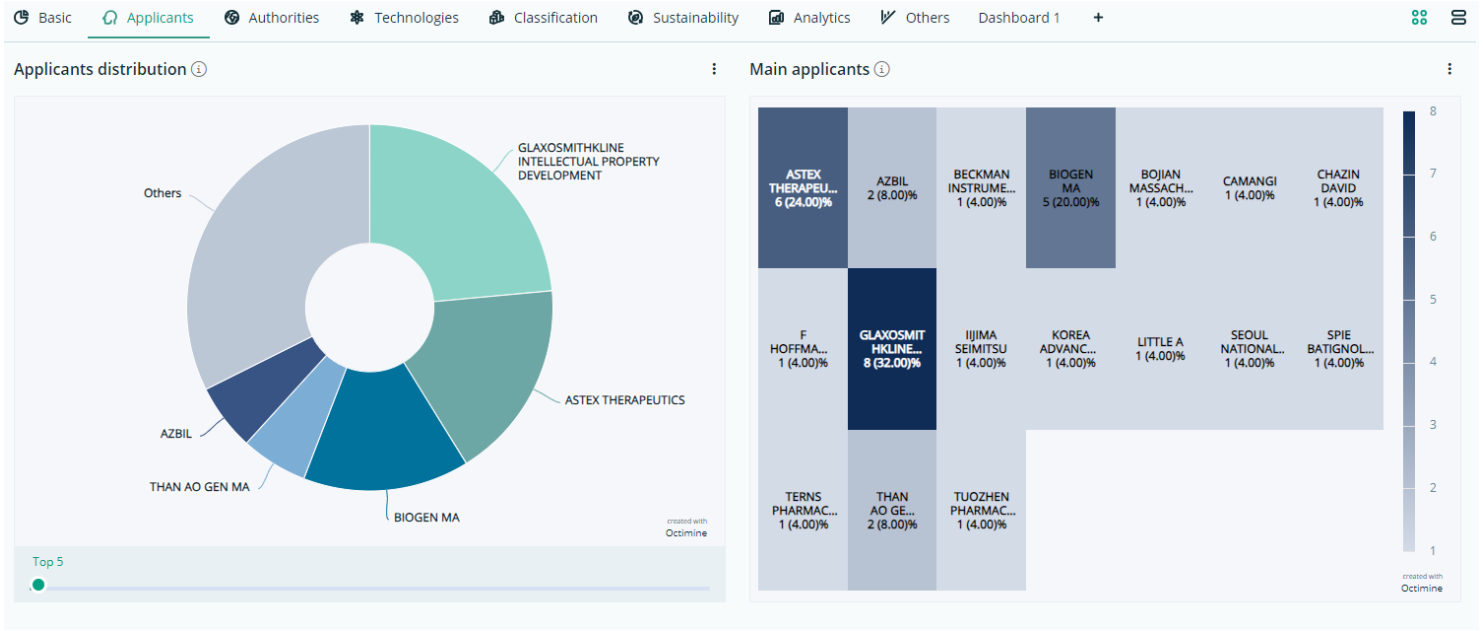

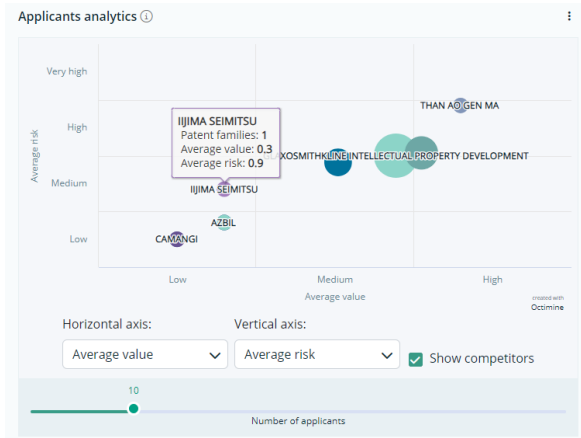

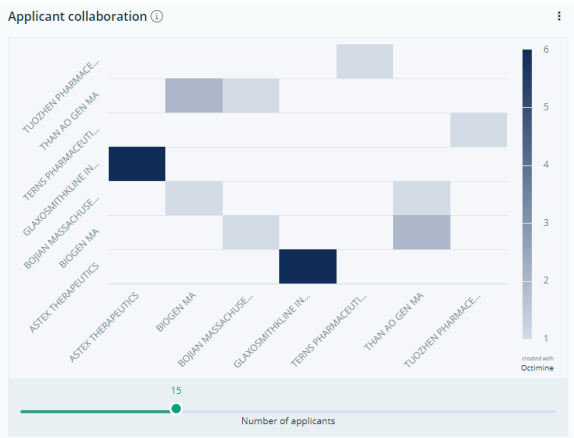

4. CURRENT LANDSCAPE OF NRF2-RELATED CLINICAL TRIALS AND PATENTS

Surge in **patent activity** for NRF2-related innovations until around 2020, followed by a sudden drop in new patents being granted.

Here are a few possible reasons for this trend

1. **Maturity of the Field** By 2020, the NRF2 research field may have reached a certain level of maturity, early discoveries and their immediate applications may have already been patented, leading to a slow-down in new filings.
2. **Shift Towards Clinical Trials** Many NRF2-related therapeutics have already reached the market. As these drugs undergo clinical trials and expand into real-world use, there may be fewer novel patent filings as the focus shifts to regulatory approvals and patient outcomes rather than new discoveries.
3. **Focus on Refinement** Instead of new patents, companies and researchers may be working on refining existing NRF2-based therapies. These may not always result in completely new patents but might instead focus on improving formulation, delivery methods, or broadening indications under existing patents.

4. CURRENT LANDSCAPE OF NRF2-RELATED CLINICAL TRIALS AND PATENTS

*Ongoing efforts to **repurpose** NRF2-based therapies for new therapeutic indications, leveraging its broad effects on oxidative stress and inflammation across multiple diseases. Here are some key examples*

*1. Dimethyl Fumarate - is now being explored for other **neurodegenerative conditions** such as **Parkinson's Disease** and **Alzheimer's Disease**, where oxidative stress plays a significant role and in **psoriasis**, taking advantage of its immunomodulatory properties (ability to reduce inflammation via NRF2 activation)*

*2. Bardoxolone Methyl - is now being tested for a broader range of **chronic diseases**, including **pulmonary arterial hypertension** and **type 2 diabetes**, conditions that are associated with inflammation and oxidative damage*

*3. N-Acetylcysteine (NAC) - is being considered for repurposing in neurodegenerative diseases like **ALS (Amyotrophic Lateral Sclerosis)** and as a potential adjunct therapy in **psychiatric disorders** such as **schizophrenia**, where oxidative stress is a contributing factor*

*4. Sulforaphane - is being repurposed for use in **autism spectrum disorder (ASD)** and **schizophrenia**, due to its role in modulating oxidative stress and inflammation, which are thought to contribute to these conditions*

4. CURRENT LANDSCAPE OF NRF2-RELATED CLINICAL TRIALS AND PATENTS

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Here are a few possible reasons for this trend

4. Regulatory and Market Considerations The drop in patent filings could also be attributed to market dynamics and regulatory environments as NRF2-targeting therapies reach regulatory approval, researchers and companies might be focusing on product development and clinical applications rather than discovery-driven patents.

5. Potential Challenges in Novel Applications Researchers may have encountered scientific or clinical challenges that make it difficult to develop completely novel applications for NRF2. The complexities in targeting the NRF2 pathway (for example, balancing its protective effects with **potential cancer risks**) may slow down the rate of patentable breakthroughs.

6. COVID-19 Impact The pandemic may have temporarily shifted research priorities towards urgent areas like vaccine and antiviral development, slowing down innovation in other fields like NRF2 research.

5. THE FUTURE OF THE NRF2 COMMUNITY

As NRF2 research progresses, the community is expected to explore several critical areas that could drive the next phase of innovation and application. Some of the key trends and future directions that the NRF2 community is likely to focus on

1. Precision Medicine and Personalised Therapies

Trend Advances in genomics and personalised medicine are expected to play a central role in the future of NRF2 therapies. Genetic variations in the NFE2L2 gene (encoding NRF2) and its regulators like KEAP1 can influence how individuals respond to oxidative stress and NRF2 activators. Thus, tailoring NRF2-based treatments to individual genetic profiles will be a focus.
Impact This personalised approach could revolutionise how diseases such as neurodegenerative disorders, cancer, and chronic inflammatory conditions are treated, leading to more effective and safer therapies

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2. Expanded Therapeutic Applications

Trend The NRF2 community is expected to investigate broader applications in diseases like autoimmune disorders, metabolic syndrome, and aging-related diseases, where oxidative stress and inflammation are central to disease progression.
Impact This could lead to the repurposing of existing NRF2 activators for new indications or the development of next-generation compounds targeting previously underexplored areas like mental health, age-related cognitive decline, and more

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3. Enhanced Collaboration and Open Science

Trend The NRF2 research community is likely to increase collaboration across multidisciplinary fields such as systems biology, bioinformatics, and pharmacology to uncover deeper insights into NRF2 regulation and its broad physiological roles.
Impact These collaborations could lead to the development of new biomarkers, improving patient selection in clinical trials, and enhancing the predictability of therapeutic outcomes. Open science initiatives will also drive innovation by sharing data, resources, and tools

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4. Overcoming Resistance and Feedback Mechanisms

Trend One of the biggest future challenges for the NRF2 community will be tackling resistance mechanisms like BACH1, which inhibits long-term NRF2 activation. Research will focus on understanding these negative feedback loops and designing compounds that can bypass or modulate them

Impact Successfully overcoming these challenges could prolong the efficacy of NRF2 therapies, especially in chronic diseases and cancer, where resistance to treatment limits therapeutic outcomes.

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5. Next-Generation NRF2 Modulators

Trend As understanding of NRF2 deepens, more refined and selective NRF2 modulators are likely to be developed. These compounds will aim to achieve specific activation or inhibition of NRF2 in targeted tissues without off-target effects.
Impact These next-generation compounds could improve the safety profile of NRF2-based therapies, particularly in long-term treatments for chronic diseases like diabetes, COPD, and cardiovascular diseases

C D E

 Communication	 Dissemination	 Exploitation	
Reach out to society and show the **impact and benefits of EU-funded R&I activities.** Targeted communication activities must address the public policy perspective of European R&I funding by considering aspects such as (i) the benefits of transnational cooperation in a European consortium or (ii) scientific excellence or (iii) contributing to competitiveness and to solving societal challenges.	**Transfer knowledge & results** with the aim to enable others to use or reuse and take up results, thus maximising the impact of EU-funded research.	**Effectively use/reuse project results** through scientific, economic, political or societal exploitation routes aiming to turn R&I actions into concrete value and impact for society.	Objective
Inform about and **promote** the **project AND its results/ success** in a non-technical manner and through strategically planned actions – possibly engaging in a two-way exchange.	**Describe** and **ensure results available** for others to **USE or REUSE** ➡ focus on results only!	**Make concrete use/reuse** of research results (not restricted to commercial use.)	Focus
Multiple audiences beyond the project's own community incl. media and the broad public.	Audiences that may take an interest in the potential **USE/REUSE** of the results (e.g. scientific community, industrial partner, policymakers).	People/organisations including project partners themselves that make concrete use/reuse of the project results, as well as user groups outside the project.	Target Audience

6. BENBEDPHAR SUSTAINABILITY PLANS

Based on the above, the BenBedPhar Community needs to identify how to sustain its engagement with key stakeholders and explore potential pathways for sustainable pharmaceutical research and development.

These may include

- continuing collaboration with public and private sectors through Public-Private Partnerships (PPP)
- advocating for policy frameworks that support sustainable innovation and patients' rights
- informing the public about NRF2 prospects
- identifying funding opportunities for the Research Community through grants from Foundations and research programmes like Horizon Europe
- promoting Innovation or engaging in the clinical settings via a Biobank

BenBedPhar can ensure that its interventions are not only scientifically innovative but also environmentally and socially responsible

6. BENBEDPHAR SUSTAINABILITY PLANS

Potential forms of BenBedPhar sustainability plans on Tech-Transfer

- ✓ **Licensing Agreements** Intellectual property (IP) rights, such as patents, are licensed to companies or other entities to develop and commercialize the technology.
- ✓ **Trade secrets** Involve protecting confidential business information - such as proprietary formulas, processes, or designs - that gives a competitive advantage without publicly disclosing the innovation.
- ✓ **Spin-offs and Startups** New companies are created to commercialize technologies developed within research institutions, often involving the original inventors.
- ✓ **Collaborative Research Agreements** Joint research projects between universities, research institutions, and industry partners aimed at developing technologies with commercial potential.
- ✓ **Consulting and Advisory Services** Researchers provide their expertise to companies to help them implement or develop new technologies.
- ✓ **Public-Private Partnerships** Government bodies and private companies collaborate to bring public-funded research into the market.
- ✓ **Material Transfer Agreements (MTAs)** Legal documents allowing the transfer of tangible research materials between institutions or companies for further development.

6. BENBEDPHAR SUSTAINABILITY PLANS

Dissemination Examples

Research Publications and Collaborations Opportunities for members to publish cutting-edge research in high-impact journals and collaborate through the network.

Technological Innovations and Commercial Partnerships The potential for developing new diagnostic tools, therapies, and AI applications in partnership with tech companies.

Policy Influence and Funding Network can influence health policy decisions and increase visibility for securing funding.

EXAMPLE

Stakeholders Analysis – Exploitation Avenues

Intellectual Property and Commercialisation

- Patents Assist Researchers to protect innovative findings or technologies through patents, which can lead to commercial partnerships or startup creation.
- Licensing Explore opportunities for licensing technologies or methodologies developed within the network to biotech or pharmaceutical companies.

Technology Transfer

- Spin-offs and Startups Support the creation of spin-off companies that can develop and market the technologies invented within the community.
- Industry Collaboration Establish formal collaborations with industry partners who can provide funding, resources, and platforms for scaling up promising technologies.

EXAMPLE

Stakeholders Analysis - Exploitation Avenues

Clinical Trials and Implementation

- Protocol Development Use the network's collective expertise to develop new clinical trial protocols, enhancing the efficiency and effectiveness of brain cancer treatments.
- Clinical Partnerships Establish Partnerships with Clinical Institutions to test new diagnostic tools and treatments developed by the network.

Data Utilisation and Software Development

- Data Sharing Platforms Develop and exploit comprehensive *own(?)* data sharing platforms that can be used by Researchers, enhancing the scope of data analysis and research insights.
- Software Tools Create proprietary software tools for data analysis, neuroimaging, or patient management, which can be licensed to hospitals and research institutions.

EXAMPLE

Stakeholders Analysis - Exploitation Avenues

Educational Products and Services

- Continuing Professional Development (CPD) Develop and offer CPD courses on the latest research, technologies, and treatment methodologies for brain cancer.
- E-Learning Modules Create e-learning modules and virtual workshops to disseminate knowledge and train researchers and clinicians across Europe.

Policy and Advocacy

- Guideline Development Work on developing new guidelines for the diagnosis and treatment of brain cancer, based on the latest research findings from the network.
- Policy Advocacy Use the network's collective voice to advocate for changes in health policy, funding priorities, and public health initiatives related to brain cancer.

THANK YOU

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COST Action CA20121

Bench to Bedside transition for Pharmacological regulation of NRF2 in non communicable diseases