Immunopharmacology: challenges, opportunities and research tools.

1-2 October 2018, Edinburgh UK

Meeting Report

Report compiled by Prof. Michael Spedding, Simon Harding, Steve Alexander, Jamie Davies, Francesca Levi-Schaffer, and the speakers.

At the beginning of October 2018 we held a meeting in Edinburgh focussed on the launch of the IUPHAR Guide to IMMUNOPHARMACOLOGY. Invited speakers contributed to productive discussions on the varying challenges and opportunities in immunopharmacology research. This meeting report summarises the presentations, discussions and outcomes.

Congratulations for the 2018 Nobel Prize for Medicine



James P. Allison

The 2018 Nobel Medicine Prize has been jointly won by James Allison of the University of Texas and Tasuku Honjo of Kyoto University (see photographs) for their work on check-point inhibitors, liberating a compromised immune system to reject cancers. Tasuku Honjo gave the inaugural address at the World Congress of Pharmacology in Kyoto. James Allison showed that the T cell protein CTLA-4 functions as a brake on T cells. and developed an antibody that could bind to CTLA-4 and block its action allowing T cells to attack cancer cells. Famously, Allison and his team showed over Christmas 1994 that mice with experimental cancers could be cured by treatment with the antibodies and by 2010 clinical trials showed remarkable effectiveness in melanoma with some patients being cured. In 1992, Tasuku Honjo had discovered PD-1 on T-cells and showed that PD-1, like CTLA-4, functions as a T-cell brake. In 2012 clear efficacy was shown in several types of cancer, with long-term remission and even cure in some cases of metastatic cancer. This has resulted in the biggest investment in clinical trials (~2000 in ClinicalTrials.gov) ever recorded for a single subject, showing the immense potential promise of this research area. IUPHAR congratulates these remarkable scientists, and also the many other scientists who have contributed to the field. Partially because of this work on check-point inhibitors, we have prioritised the growing field of immunopharmacology.



Tasuko Honjo

Immunopharmacology: The New Frontier

There has been immense progress in immunopharmacology, but there are insufficient links between the immunological and pharmacological sciences. Thus, we have set up several initiatives.

- IUPHAR set up an immunopharmacology section (Immuphar) chaired by Francesca Levi-Schaffer.
- IUPHAR has signed an agreement with International Union of Immunological Sciences (IUIS, President Alberto Mantovani, who has also made major contributions to the field of check-point inhibitors) to ensure collaboration and cooperation.
- IUPHAR, NC-IUPHAR (chair Steve Alexander), the University of Edinburgh (PI, Pr Jamie Davies) and the Edinburgh database group (IUPHAR/BPS Guide to Pharmacology; www.guidetopharmacology.org) have been able to set up a new database on the drug targets in immunopharmacology, financed by a major grant from the Wellcome Trust. This is www.guidetoimmunopharmacology.org, which has been recently launched and is freely available to all. The BPS finance two staff in the Edinburgh group for which IUPHAR is immensely grateful.
- To celebrate this launch, a focussed immunopharmacology meeting was organised, which included the Anthony Harmar memorial lecture. This report provides a a summary of the meeting presentations, discussions and outcomes.

Meeting Presentations

Anthony Harmer Memorial Lecture: Decision-making in lung immunity	**Prof. Tracy Hussell**
The Guide to IMMUNOPHARMACOLOGY	Dr. Elena Faccenda, Dr. Chris Southan and Dr. Simon Harding
Macrophage plasticity in immunopathology and cancer: from bench to bedside	Prof. Alberto Mantovani
Targeting Pattern Recognition Receptor signalling for therapeutic approaches	Prof. Clare Bryant
Discovering the right target in inflammatory disease	Prof. Iain McInnes
Is Atherosclerosis a Systemic or a Vascular Immune Disease?	Prof. Pasquale Maffia
Inhibit Activation or Activate Inhibition of Mast Cells and Eosinophils: Which Weapon is Better to Fight Allergic Diseases?	Prof. Francesca Levi-Schaffer
IUPHAR: natural products and immunology	Prof. Michael Spedding
Human type I interferon up regulation - worth targeting?	Prof. Yanick Crow
A review on kinase targets in immunological indications	Dr. Dorian Fabbro

Anthony Harmer Memorial Lecture: Decision-making in lung immunity



Prof. Tracy Hussell, University of Manchester, UK

Tracy Hussell is Director, Manchester Collaborative Centre for Inflammation Research (MCCIR) and Professor of Inflammatory Disease, University of Manchester

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To be healthy is an active process so health must be continually maintained. Is disease a process that can't sense it is healthy again? We all have different set points. Sterile inflammation can be created by a single missing factor. Generally, while the lung epithelium is intact, then the tissue is non-activated. Epithelial damage is a critical driver, which may permanently change macrophages and the basal state in the lung. Airways macrophages are critical - when washed out, tissues change very quickly.

CD200R transmits negative signal to macrophages and ligand is on epithelium cells. Then antigen relieves signal. Axl continually recognises gas 6 on apoptosis so don't activate with apoptosis.

Resolution of inflammation gives a different macrophage population – twice as many as before inflammation, which may survey the environment, resolving from a severe inflammatory event, to a new state. There are therapeutic ways of going back, but chronic obstructive pulmonary disease (COPD) and asthma have a permanently active state. MiRNAs are changed in resolved inflammation, therefore let-7b is increased, modifying Toll response changes. Patient becomes less responsive to bacteria - patients are retuned to not die when challenged, but have also lost miRNAs. The basement membrane is normally very thin but becomes permanently changed (Burgstaller et al, 2017, Eur Respir J. 2017 doi: 10.1183/13993003). The tissue is changed, so not just immune effects.

Hyaluranon is a major constituent of the inflamed lung. Is the lung inflamed or is it just because there are a lot of retained immune cells? The latter. Why does matrix persist? Hyaluronic acid synthase is increased (clearance unchanged, hyaluronase unchanged). Matrix turnover means that there are more activated immune cells. The impact of viral infections on lung matrix affects its mechanical stability and structural support. The composition of matrix also indirectly controls inflammation by influencing cell adhesion, migration, survival, proliferation and differentiation. Hyaluronan is a significant component of the lung extracellular matrix and production and degradation must be carefully balanced. Tracy discovered an imbalance in hyaluronan production following resolution of a severe lung influenza virus infection, driven by hyaluronan synthase 2 from epithelial cells, endothelial cells and fibroblasts. Furthermore hyaluronan, due to elevated TNF, sequesters CD44-expressing macrophages. Intranasal hyaluronidase reduces lung hyaluronan restoring function. Hyaluronidase is already used clinically. Digestion of HA restores lung function. Hyaluronidase (available for clinical trials) appears an interesting option (Hussell T et al., Eur Respir Rev. 2018, 27(148))

In cancer the matrix is abnormal, and the immune system is paralysed. In many instances the matrix is stiff. It may be possible to think differently about reactivating the immune system here.

In severe cell death, macrophages clear apoptotic cells, TAMs recognise external phosphatidyl serine. Reverse signalling to STAT1 turning off inflammation, so while apoptosis is going on the tissue is vulnerable to bacterial attack. Axl receptor only in lung so this represents a unique opportunity for targeted therapy. Changed matrix, lost apoptosis, but poorly cleared even if immunity suppressed.

Eight days after influenza, basal cells proliferate requiring Axl receptor to show that damage has happened. Basal cell show hyperplasia if apoptosis continues – most lung disease has this as a hallmark. Axl antagonists allows faster repair. Type 1 interferons (IFNs): Neuropeptide receptors alter away homeostasis Gfra2 part of GDNF family massively increased on lung TAMs. Needs to co-stimulate with ret which is induced by type 1 IFNs. The virus may act via TLR7/8, in epithelium. MMP2 is specifically increased to degrade collagen type IV to degrade basement membrane. Two chemokines bind CXCR2. CCL18 macrophages that drive resolution, no homologue in rodents.

Is COPD then associated with inflamed tissues or trapped inflammatory cells? Possibly like tumours. Will check-point inhibitors also release antigen presenting cells? New therapeutic options await validation.

The Guide to IMMUNOPHARMACOLOGY

Dr. Elena Faccenda, Dr. Chris Southan and Dr. Simon Harding

University of Edinburgh

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The International Union of Basic and Clinical Pharmacology (IUPHAR) Guide to IMMUNOPHARMACOLOGY (www.guidetoimmunopharmacology.org) is a new, Wellcome Trust-funded, open-access resource that brings an immunological perspective to the high quality, expert-curated pharmacological data found in the existing IUPHAR/British Pharmacological Society guide to pharmacology (www.guidetopharmacology.org).

Chris, Elena and Simon presented the resource, marking its official launch after 3 years of development. Chris and Elena illustrated how existing targets and ligands of immunological relevance have been identified and curated into the resource. In total, over 540 targets and 1,000 ligands are now tagged in the database as being relevant to immunopharmacology. It was also shown how new associations to immunological data type have been incorporated. To date we have curated approximately 300 associations between targets and immune cell types; approximately 3,000 associations between targets and immune or inflammatory system processes; approximately 53 associations between targets and immunological diseases; and approximately 700 associations between ligands and immunological diseases.

Simon presented a live demonstration of the resource, illustrating how the website has been updated to provide an immune-specific view of the underlying pharmacological data, such that users can easily find and see targets and ligand of immunological relevance and so that users can browse and search via new immunological data types.

Macrophage plasticity in immunopathology and cancer: from bench to bedside



Prof. Alberto Mantovani, Humanitas University, Italy

Alberto is president of the International Union of Immunological Societies (IUIS)

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It was very fitting that as Alberto gave his talk, the Nobel prize for check-point inhibitors was announced. Tumour-associated macrophages (TAMs) are pivotal players of the tumour microenvironment and, being plastic contribute differently various phases of cancerogenesis. Tumour-associated neutrophils (TANs) are also emerging as important components of the tumour microenvironment, given their unexpected heterogeneity and plasticity. TAMs and TANs are both integrated in cancer-related inflammation. TANs, are the major contributors of highly angiogenic MMP-9, whereas precursors of macrophages arriving in tumours, require time to differentiate, polarize into M2-skewed TAMs, shut down their TIMP-1 expression.

TAMs can exert a yin-yang influence on the effectiveness of chemotherapy and radiotherapy, either antagonizing the anti-tumour activity of these treatments by orchestrating a tumour-promoting, tissue-repair response or, instead, enhancing the overall antineoplastic effect. Reviewed in the attached paper. TAM may create an immunosuppressive environment in tumours through multiple routes including triggers of checkpoint blockade in T cells.

Therapies

Nanomedicines can be directed against TAMS. Development of TAM-targeted imaging nanostructures can be used to study the macrophage content in solid tumours and, hence, for a better diagnosis and prognosis of cancer disease.

IL-4 and IL-13 are involved in tissue repair and protumour, extremes in a universe of states, contributing to the ping-pong interaction between tumour cells and macrophages. Chronic non-resolving inflammation (inflammaging) is a factor. TAMs activity is skewed from signals from tumor cells (particularly in pancreatic and breast cancer). TAMs suppress immune system and induce checkpoint blockade. In Hodgkin's lymphoma, tumour cells express PD1 directly as do macrophages. The inflammatory cytokine, IL1β skews TAMs TANs, and IL1 deficient mice are partially protected. The >10,000 patient Cantos trial showed benefit.

Trabectedin, via activating TRAIL depletes tumour promoting macrophages.

Downstream from IL-1β, long pentaxtrin3 (PTX3) is a covalently linked octamer and is a functional ancestor of antibodies, binds microbes and interacts with the complement cascade. It binds to aspergillus, P aeruginosa, and is essential for tissue repair. Polymorphisms of PTX3 yield susceptibility to aspergillus. Relevance for carcinogenesis – oncosuppresive, but only on the inflammatory aspect of cancer promotion. Unleashes a complement cascade. Combining complement block with antiPD-1, may yield protection against metastasis.

IL18 drives natural killer (NK) cell activation and differentiation via the receptor IL-1R8. IL1R8 is a major negative regulator, IL-R8 knock-out is resistant to liver carcinogenesis (but this is normally driven by inflammation). NK cells express high levels of IL1-1R8. Lung and liver have many NK cells, so IL-1R8 is a key regulator of NK cell differentiation in lung and liver. So, it may be a checkpoint inhibitor for NK cells.

IL18 drives NK activation and differentiation

IL1R8/TIR8/SIGIRR - looked like a negative regulator for IL18? Like IL37 receptor recognition, anti-inflammatory.

IL1R8 major negative regulator, R8KO resistant to liver carcinogenesis (but this is normally driven by inflammation). NK cells express high levels of IL1-1R8. Lung and liver have plenty of NK cells, so IL-1R8 is a key regulator of NK cell differentiation in lung and liver. So, a checkpoint inhibitor for NK cells.

Targeting Pattern Recognition Receptor signalling for therapeutic approaches

Prof. Clare Bryant, Univeristy of Cambridge, UK

Clare was the senior author on the definitive IUPHAR article on innate pharmacology, drug targets : pattern receptors (Bryant CE et al, Pharmacol Rev, 67, 462-504). Using single cell signalling, she defined TLR4 receptor modulation of MyD88, NFkB to drive IFNs.

Toll-like receptor signalling was previously thought to be a binary process that is either on or off. The lipid A in lipopolysaccharide (LPS) fully activates TLR4, but other lipid molecules can induce much lower levels of TLR4 activity which is not compatible with this binary model. She used single cell image analysis to analyse NFKB activation (RelA linked to green fluorescent protein), and TNFa reporter linked to m-cherry. Signalling strength is response to TLR4 activation correlates with the speed of translaocation of NfKB into the nucleus. Single molecule fluorescence analysis whereby each TLR4 molecule has one fluorescent lab showed that TLR4 exists as monomer or preformed dimer even without stimulation. LPS stabilises the preformed dimers. No TLR4 clusters are formed with lipid stimulation of TLR4. The downstream TLR signalling complex is called the MyDDosome. Using single molecule fluorescence approaches with labelled MyD88 MyDDosomes formed in response to TLR4 stimulation with signalling strength being dependent upon the speed and number of MyDDosomes formed. When stimulated with high doses of LPS super MyDDosomes formed whereby 2 MyDDosomes cluster together.

Microglia and neuroinflammation: TLR4 and synuclein (TLR4 regulated by Trem2 and ApoE)

TLR4 expression is highest within human substantia nigra so may be involved in the pathogenesis of Parkinson's disease. Small alpha-synuclein oligomers induced a TLR4-dependent sensitized inflammatory response with time, including TNF-α production. ROS and cell death in primary neuronal cultures were significantly reduced by TLR4 antagonists so cytokines produced by glial cells make a major contribution to neuronal death. Prolonged exposure to low levels of alpha-synuclein oligomers sensitizes TLR4 responsiveness in astrocytes and microglial, possibly being a cause of Parkinson's (pM works over 50-150 hours by an apparent priming response). The TLR4 antagonist *Rhodobacter sphaeroides* lipid A blocks the synuclein priming response.

Discovering the right target in inflammatory disease

Prof. Iain McInnes, University of Glasgow, UK

There is a major human-mouse divide in that IL17 is a remarkable therapy for mice. Whereas IL1beta, and interferons are greatly increased in synovial fluid, antagonist drugs have failed. A major issue is not to wait for tissue damage, treat early. Intervene late and inflammation can be blocked but damage is irreversible, as in IFN therapy for lupus. Rheumatoid arthritis (RA) is still a drug target, drug resistance for RA has 2x the number of patients of MS. RA phase F is a well-established disease phase, and is used too often in clinical trials. Phase A&B – genetic and environmental risk factors may be more useful.

Late stage studies

- New cytokine therapies, IL6 ligand failed at the last minute (just a few more deaths in treated).
- RA studies of GM-CSFR antagonists: mavrilimumab, Golimumab.
- What will JAK inhibitors tell us about RA? Tofacitinib JAK1/3i inhibitor. More likely to respond if no previous drug exposure.
- SELECT-BEYOND (Genovese et al., Lancet 2018, 391(10139), P2513-2524), upadicitnib JAK1 semi-selective, "effective in treating rheumatoid arthritis symptoms in patients with moderate-to-severe active disease with inadequate response to bDMARDs"
- GnRH antagonist Kass 2014, 14% of patients responded and CRP down, phase II ongoing.
- Biostimulators of vagus downwards to spleen to prevent inflammation.
- First mesenchymal stem cell in phase I Alvaro-Gracia.

Early stage inhibitors

- Immune tolerance studies. Trying to define biomarkers of tolerance.
- Dendritic cells may be injected back into knees after giving a tolerance-inducing therapy.
- Abatacept and rituximab IL23 inhibitors work, TNFi, JALi,IL6i, GMCSFi.
- The macrophage metabolome is a subject of great interest.
- Scottish precision medicine ecosystem SERA is Scottish early RA/UA cohort.
- **Chromosome conformation loop** – need which promoters are joined up.
- In RA 123 genetic loci looked at non-responders to methotrexate, 90% of predicting!!!
- Rituximab responsiveness.
- JAK inhibition give higher incidence of shingles in Japanese/Chinese.
- Splice variants of NLRP3 exist in humans, not in mice.
- TNF IL6 IL1 plus inflammasome activator – mouse = human, otherwise not

Is Atherosclerosis a Systemic or a Vascular Immune Disease?

Dr. Pasquale Maffia, University of Glasgow, UK

Glasgow has the worst incidence of chronic inflammation and cardiovascular (CVS) disease in the UK – there are 92000 CVS interventions in UK pa. Whereas CVS disease is reducing in the UK, in Mumbai: 60% of deaths are CVS related. India now proposes a very cheap generic polypill for all from the age of 50. CVS disease is now an African, Russian and Indian disease (60% incidence in India). The CANTOS (IL1beta) and low dose methotrexate (CIRT) trials are encouraging.

In mouse blood vessel adventitia, the arterial tertiary lymphoid organ shows activation of T cells with a high preponderance of T regs. Naïve T cells are present in non-atherosclerotic aorta. Immune response is fundamental, the aortic tertiary lymphoid organ (ATLO), is an organised lymphoid organ within the vessel. ATLOs only develop in the presence of plaques. ATLOs orchestrate dichotomic, territorialized, B-cell responses in the diseased aorta producing local antibodies (Abs); germinal centre reactions lead to generation of autoimmune B cells within the diseased arterial wall during aging. There is a dialogue between antigen presenting cells and T cells interact in adventitia as in lymph nodes. Activated Tregs are the majority of cells (knock down of Tregs make atherosclerosis worse). We need: early diagnosis, unable to assess plaque stability. As dissecting aorta is precisely defined, much research focuses on the plaque, but imaging the ATLO would be very important.

Selective deletion of MHCII in plasmacytoid dendritic cells (pDCs). pDCs can be antigen-presenting cells in the plaque and may release interferons (IFNs). So, the effects are local and early or late-stage, where different pharmacology may be needed, as plaques may be very different in their stability and immunological profile.

Inhibit Activation or Activate Inhibition of Mast Cells and Eosinophils: Which Weapon is Better to Fight Allergic Diseases?

Prof. Francesca Levi-Schaffer, Hebrew University of Jerusalem, Israel

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The pivotal effector cells of allergic inflammation are the mast cells and the eosinophils. Mast cells, as activated by IgE mechanisms via allergens, are the recognized primum movens while eosinophils infiltration and persistence in the inflamed tissue with the mast cells are the accepted features of the late stage and of the chronic outcome of allergy.

During the years we have defined a pro-inflammatory cross-talk between these two cells that we have named the Allergic Effector Unit (AEU). We found that mast cell/eosinophil interactions result in increased eosinophils chemotaxis, survival, degranulation, cytokine production and in mast cell survival, IgE-dependent and independent degranulation and cytokine production. These effects are mediated by both released mediators (soluble interactions) and by receptor/ligands binding (physical interactions). Prominent players of the activating "physical" AEU are the two activating receptors (ARs)/ligands CD48 and 2B4. Nevertheless, we have also described the presence and functional activity of two inhibitory receptors (IRs), i.e. CD300a and Siglec-7, on mast cells and on eosinophils that can indicate a possible anti-inflammatory or even pro-resolution activity within the AEU and globally as mediated by mast cells and by eosinophils.

The goal of our research is to define potential new targets for immunopharmacological intervention in allergic diseases by blocking ARs, i.e. CD48, or by activating IRs, i.e. CD300a and Siglec-7. We indeed found that CD48 is significantly upregulated on human and murine asthma on mast cells and eosinophils and in the presence of S. aureus, the prominent bacteria infecting atopic tissues. We have therefore studied CD48 modulation in vitro and in vivo and the outcome of its blockade and found that CD48 is a key player in allergic diseases. Similarly, we have found that CD300a and Siglec-7 are expressed by eosinophils and mast cells of allergic patients and described their role in downregulating these cell functions.

Thus, our strategy is to treat allergy by inhibiting activation and/or by activating inhibition of mast cells, eosinophils and the AEU. Translationally this strategy will have to take into account the allergic patient endotype.

IUPHAR: natural products and immunology

Prof. Michael Spedding, Spedding Research Solutions SAS, France

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Michael Spedding reviewed the activities of IUPHAR and the agreement with IUIS, and then discussed why despite the fact that there are 613,220 publications in Pubmed (at end of September 2018) on natural products, 21,354 of which coupled to 'inflammation', and 37,813 coupled to 'cytokines', there virtually no clinical trials ongoing combining natural products with check-point inhibitors. However, very recently new work is describing preclinical effects on check-points (PD-1, PD-L1, CTLA-4), and this is a potential area of expansion. IUPHAR and IUIS wish to expand this area of research in the developing world by proposing simple immunopharmacological protocols which can be used in preclinical and clinical research.

Human type I interferon up regulation - worth targeting?

Prof. Yanick Crow, University of Edinburgh, UK

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The comments on Yanick's talk are also associated with dial-in comments obtained during the meeting from Heinfried Radeke.

Innate immunology is crucial in viral recognition: how to differentiate nucleic acid from non-self nucleic acid, host mutations may give non-self-recognition. They support reclassifying several diseases as interferonopathies AND several common neurodegenerative diseases may be exacerbated by local interferon signalling.

Type I interferons (IFNs) are produced by plasmacytoid dendritic cells (pDCs) which are an important antiviral defence systems, which may well go awry in several human diseases. The sheer number of commensal versus pathogenic viruses which the immune system is exposed to is incredible. They express intracellular Toll-like receptors 7 and 9 which detect ssRNA and CpG DNA motifs, respectively. They can be activated by invasive viruses, abnormally degraded DNA and retroviruses. As pDCs can produce ~1000 fold more IFN-α than other cells, they can have a targeted role in antiviral defense but if they respond to other stimuli including HERVs then these high local concentrations of IFN-α, lead to “type 1 interferonopathies”. Classically these are: recruitment to skin (SLE), to muscle (dermatomyocytis), and to salivary glands (Sjögren’s Syndrome) and brain (encephalopathy in Aicardi-Goutieres syndrome - AGS). However, not only viruses can recruit PDCs but also defective host nucleic acid clearance, due to mutations, or interplay between mutations and viruses. Retrotransposons can also activate IFN-α.

There are a suite of disorders linked to excess production of IFNs. The are major interactions between genome and infection, essentially involving inappropriate DNA/RNA repair.

Between 2006 and 2012, mutations in 6 different genes were described to be associated with Aicardi-Goutières syndrome (paediatric brain calcification and demyelination), specifically-TREX1, RNASEH2A, RNASEH2B, RNASEH2C, ADAR, and SAMHD1, as these are involved in DNA/RNA repair then mutations may blur the line between self and non-self. More recently, mutations in IFIH1 were reported in a variety of neuroimmunological phenotypes, including Aicardi-Goutières syndrome, while a specific Arg822Gln mutation in IFIH1 was described in 3 discrete families with Singleton-Merten syndrome (SMS). IFIH1 encodes for melanoma differentiation-associated gene 5 (MDA5), and all mutations identified to date have been associated with an enhanced interferon response in affected individuals.

Other discussion points

- Type1 interferonopathies may be an upreg of disease pathogenesis.
- Aicardi-Goutieres syndrome. TREX1, RNAaseH2A, SAMHD1, ADAR
- Assays can now see fmol/mg IFN, and patients with mutations in these genes show increased blood IFN
- Involved in DNA or RNA metabolism, STING accessory for DNA sensing in the cytoplasm.
- USP18 and ISG15, downregulate IFN.

- Proteosome molecules are relevant? Mitochondrially double stranded RNA, and don't confuse for virus. Self-waste disposal, self-marking. Edit ADARs most gain of function in sensor, of MDA5
- Phenotypes are extremely broad. TREX1, clinical non-penetrance.
- Nucleic acid driven mutations. Adaptive immune disease.
- CNS: Brain infection with Zika increases intracranial calcium; AGS v similar due to type I IFN signalling

Links with mitochondrial dysfunction

Mitochondrial DNA in the cytoplasm activates STING which is a major cause of neuroinflammation and may be critical in Parkinson's disease. Very recently, Sliter et al, Nature 13/9/18, 561, 258) showed that Parkin and PINK1 protect against STING-induced inflammation. Impressive role of STING: Gain-of-function mutations in transmembrane protein 173 (TMEM173) encoding stimulator of interferon genes (STING) were shown to cause type I interferonopathy: STING-associated vasculopathy with onset in infancy (SAVI). STING gain of function induces terrible rheumatological diseases (skin, lung). Li et al (2011) showed clear hyperactivation of JAK-STAT1 signalling pathway and negative feedback down-regulation of SOCS-1 in in the monocytes from patients with lupus. Therefore JAK 1 and 2 inhibitors, work on very well on TREX1 mutation skin lesions.

Treatment - JAK inhibitors, or antivirals

Crow has shown in clinical studies that he initiated that the use of reverse transcriptase inhibitors may be benficial: TREX1 in line1 inhibitors. Reverse transcriptome inhibitors work as in HIV, in IFN score; 8/9 patients showed abig reduction in IFN score. Score normalised in two patients. IFN protein in CSF down and after treatment was stopped the effect reversed.

Progressive spastic paraparesis (PSP) is associated with intracranial calcification and upregulation of interferon-stimulated gene transcripts and a heterozygous IFIH1 c.2544T>G missense variant (p.Asp848Glu, gain of function) segregated with interferon status; thus, PSP is an IFIH1-related type 1 interferonopathy. He also defined type I interferonopathy due to DNase II deficiency in humans. Singleton-Merten syndrome, Jaccoud's arthropathy and neuroinflammation may be due to MDA-5 gain-of-function lead to type I interferonopathy disease spectrum.

Heinfried Radeke had previously shown a potential link with tissue-resident macrophages/lymphocytes. Gebhardt 2018 showed that there were also tissue-resident lymphocytes, surveilling locally. Resident T cell infiltration of previously infected tissues is retained, with the cells sitting in the tissue and looking for infection, so 'ready to go'. CD69 is a key driver. These resident cells are fingolimod insensitive – **with CD69 being highly expressed, and associated with Th17 profiles**. KLF2 and 3 up, SIP 5 doesn't regulate these cells therefore they don't egress the tissue.

The cells are regulated by TGFbeta IFNbeta, IL33, 1L12, p70. So S1P1 and S1P5 specific drugs are being studied. Fingolimod has some effects nevertheless, due to less stimulation of new cells arriving.

Interferon is a strong stimulant of CD69. So plasmacytoid dendritic cells (PDCs, just a few, even two - ten) can get together around a viral or mutation-driven signal when activated and produce massive quantities of Interferon alpha. This IFN increases CD69 in tissue-resident lymphocytes which are

‘waiting to go’. So, this could be the missing link for interferonopathies in Sjogren’s, lupus, etc. and it is possible that some neurodegenerations may be interferonopathies. However again only about 40% of patients have circulating IFNs, but local tissue IFN is much more difficult to measure. This reinforces the necessity to dose PDCs in tissues, and favours at least some aspects of these diseases being related to local excess IFN production. It may be a crucial link into neuroinflammation.

A review on kinase targets in immunological indications

Dr. Doriano Fabbro, Piqur Therapeutics, Switzerland

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Doriano Fabbro gave a complete overview of kinase inhibitors in therapy. In the oncology arena there around 50 Kinase inhibitors approved and many more in clinical trials (400 clinical trials are ongoing worldwide). However, the kinase targets are not spread-out very largely and the pharmaceutical industry has only a few kinase targets on the radar and have produced multiple inhibitors for the same target and indication. This was also due to the optimization of the compound for the target and the consequences of the target-related resistance that very often ensues following treatment of cancers with a particular kinase inhibitor. Thus first, second and third generation kinase inhibitors have been designed, tested in the clinic and approved. The consequence of this is that the Kinase inhibitors are now named according to their primary target or example JAKinibs (JAK inhibitors), HERinibs (EGFR inhibitors), ABLinibs (ABL inhibitors), ALKinibs (ALK inhbitors) etc. (see table 1).

In contrast, in the non-oncological indication only a handful of kinse inhbitors have been approved like the mTOR inhibitor everolimus for transplantation and stents, the ROCK inhibitor Fasudil for cerebral vasospasms, the JAK inhibitors Tofacitinib and Baricitinib for RA, the SYK inhibitor Fostamatinib for ITP and the multikinase inhibitor Nintedanib for IPF.

Year	Generic name (compound code, Trade names)	Kinase Target	Disease	Company (year, type)	Class
1995	Fasudil (HA-1077) [5181]	ROCK1/2	Cerebral vasospam, PAH	Asahi Kasei (1995, type-1)	
1999	Sirolimus (Rapamune) [6031]	mTOR	Kidney transplants	Pfizer, Wyeth (1999, type-3)	Rapa
2001	Imatinib (STI571, Glivec, Gleevec) [5687]	ABL, PDGFR, KIT	CML, Ph+ B-ALL, CMML, HES, GIST	Novartis (2001, type-2)	ABLinib
2003	Gefitinib (ZD1839, Iressa) [4941]	EGFR	NSCLC	AZ (2003, type-1)	HERinib
2004	Erlotinib (OSI-774,Tarceva) [4920]	EGFR	NSCLC, pancreatic cancer	Roche, OSI (2004, type-1)	HERinib
2005	Sorafenib (BAY 43-9006, Nexavar) [5711]	VEGFR2, PDGFR, KIT, FLT3, BRAF	RCC, HCC	Bayer, Onyx (2005, type-2)	Multi
2006	Sunitinib (SU11248, Sutent) [5713]	VEGFR, KIT, PDGFR, RET, CSF1R, FLT3	RCC, imatinib resistant GIST	Pfizer (2006, type-1)	Multi
2007	Lapatinib (GW2016, Tykerb) [5692]	EGFR, ERBB2	BC	GSK (2007, type-1.5)	HERinib
2007	Dasatinib (BM-354825,Sprycel) [5678]	ABL], PDGFR, KIT, SRC	CML	BMS (2007, type-1)	ABLinib
2007	Nilotinib (AMN107,Tasigna) [5697]	ABL, PDGFR, KIT	CML	Novartis (2007, type-2)	ABLinib
2009	Everolimus (Rad001, Certican, Zortress, Afinitor, Votubia) [5889]	mTOR	RCC, SEGA, Transplantation	Novartis (2009, type-3)	Rapa
2009	Temsirolimus (CCI-779, Torisel) [5892]	mTOR	RCC	Pfizer, Wyeth (2009, type-3)	Rapa
2011	Crizotinib (PF-02341066, Xalcori) [4903]	MET and ALK	NSCLC with ALK translocations	Pfizer (2011, type-1)	ALKinib
2011	Vandetanib (ZD6474, Caprelsa) [5717]	RET, VEGFR1-2, FGFR, EGFR	MTC	AZ (2011, type-1)	RETinib
2011	Ruxolitinib (INC424, Jakafi) [5688]	JAK2	IMF JAK2V617F	Novartis, Incyte (2011, type-1)	JAKinib
2011	Vemurafenib (PLX4032, RG7204, Zelboraf) [5893]	BRAF	Metastatic melanoma BRAFV600E	Roche, Plexxikon (2011, type-2)	RAFinib
2011	Axitinib (AG013736, Inlyta) [5659]	VEGFR, KIT, PDGFR, RET, CSF1R, FLT3	RCC	Pfizer (2012, type-1)	Multi
2012	Regorafenib (BAY 73-4506, Stivarga) [5891]	VEGFR2, Tie2	CRC, GIST and HCC (2017)	Bayer (2012, type-2)	Multi
2009	Pazopanib (GW-786034, Votrient) [5698]	VEGFR, PDGFR, KIT	RCC	GSK (2012, type-1)	Multi
2012	Tofacitinib (CP-690550, Xeljanz Tasocitinib) [5677]	JAK3	RA	Pfizer (2012, type-1)	JAKinib
2012	Cabozantinib (XL184, BMS907351, Cometriq) [5887]	VEGFR2, PDGFR, KIT, FLT3	MTC	Exelexis (2012, type-1)	Multi
2012	Ponatinib (AP24534, Iclusig) [5890]	ABL	Imatinib resistant CML ABL-T315I mutations	Ariad (2012, type-1)	ABLinib
2012	Bosutinib (SKI-606, Bosulif) [5710]	ABL	CML resistant/ intolerant to therapy	Pfizer (2012, type-1)	ABLinib
2013	Dabrafenib (Tafinlar) [6494]	BRAF	Metastatic melanoma with BRAFV600E	GSK (2013, type-1.5)	RAFinib
2013	Trametinib (Mekinist) [6495]	MEK	Met melanoma with BRAFV600E mutations	GSK (2013, type-3)	MEKinib
2013	Afatinib (Gilotrif, Tomtovok, Tovok) [5667]	EGFR	NSCLC with EGFR activating mutatior	BI (2013, covalent)	HERinib
2013	Ibrutinib (PCI-32765, Imbruvica) [6912]	BTK	MCL, CLL	Janssen, Pharmacyclic (2013, covalent)	BTKinib
2014	Ceritinib (LDK378, Zykadia) [7397]	ALK	NSCLC with ALK translocations	Novartis (2014, type-1)	ALKinib
2014	Idelalisib (CAL101, GS1101, Zydelig) [6741]	PI3Kdelta	CLL, FL and SLL	Gilead, Calistoga, ICOS (2014, type-1)	PIKlisib
2014	Nintedanib (BIBF 1120, Vargatef, Intedanib) [5936]	VEGFR, PDGFR, FGFR	Idiopathic Pulmonary Fibrosis	BI (2014, type-1)	Multi
2014	Alectinib (AF802, Alecensa) [7739]	ALK	ALK-transloctaed NSCLC (brain mets)	Roche, Chugai (2014, type-1) japan	ALKinib
2015	Palbociclib (PD-0332991, Ibrance) [7380]	CDK4/6	Advanced (metastatic) BC	Pfizer (2015, type-1)	CYClib
2015	Lenvatinib (E7080, Lenvima) [7426]	VEGFRs multikinase	Thyroid cancer (DTC); Kindney cancer	Eisai Co (2015, type-1)	Multi
2015	Cobimetinib (GDC-0973, XL-518, Cotellic)	MEK	Melanoma in combination with vemurafenib	Roche, Exelexis (2105, type-3)	MEKinib
2012	Radotinib (Supect, IY5511)	BCR-ABL, PDGFR	CML	Daewoong Pharmaceutical (2015, type-2) SK	ABLinib
2015	Osimertinib (Mereletinib, AZD9291; Tagrisso)	EGFR (T790M)	NSCLC with EGFR-T790M	AZ (2015, covalent)	HERinib
2016	Olmutinib (HM-61713, BI-1482694	EGFR (T790M)	NSCLC with EGFR-T790M	Boehringer Ingelheim/Hanmi)	HERinib
2017	Ribociclib (LEE011; Kisqali)	CDK4/6	1st-line HR+/HER2- metastatic BC in combo with any AI	Novartis (2017, type-1)	CYClib
2017	Brigatinib (AP26113, Alunbrig)	ALK and EGFR	ALK-rearranged and EGFR-T790M NSCLC	Ariad (2017, type-1)	ALKinib
2017	Midostaurin (PKC412, CGP41251, Rydapt)	FLT3, KIT	AML, Mastocytosis	Novartis, (2017, type-1)	Multi
2017	Neratinib (HKI-272, Nerlynx)	EGFR	BC-HER2 overexpressed after trastuz	Wyeth, Pfizer -> Puma (2017, covalent)	HERinib
2017	Baricitinib (Olumiant, INCB28050, LY3009104)	JAK1/JAK2	RA	Incyte/Eli Lilly	JAKinib
2017	Abemaciclib (LY2835219, Verzenio)	CDK4/6	1st-line HR+/HER2- metastatic BC in combo with any AI	Eli Lilly (2017, type-1)	CYClib
2017	Copanlisib (BAY 80-6946, Aliqopa)	dual PI3K/mTOR	FL	Bayer (2017, type-1)	PIKlisib
2017	Acalbrutinib (ACP-196, Calquence)	BTK	MCL	AZ, Acerta Pharma (2017, covalent)	BTKinib
2818	Fostamatinib (R-406, Tavalisse)	SYK	Idiopathic Thrombocytopenic Purpura	Rigel (2018, Type-1)	SYKinib
2018	Simotinib	EGFR	NSCLC patients with EGFR	Jiangsu Simcere Pharmaceutical. C	HERinib
2018	Binimetinib (MEK162, Mektovi) with Encorafenib (LGX818, Br	MEK/RAF combo	Melanoma	ARRAY (2018, type-3) Novartis (2018, type-2)	MEKinib
2018	Duvelisib (IPI-145, Copiktra)	PI3Kdelta/gamma	CLL and SLL	Infinity, Verastem (2018, type-1)	PIKlisib
2018	Dacomitinib (PF-00299804, Vizimpro)	EGFR	NSLSC with EGFRmut	Pfizer (2018 covalent)	HERinib

Table 1: Naming of Kinase inhibitors according to their primary target or example JAKinibs (JAK inhibitors), HERinibs (EGFR inhibitors), ABLinibs (ABL inhibitors), ALKinibs (ALK inhbitors) etc. Download as PDF.

There are at least around 50 kinase targets that would make sense to develop inhibitors for clinical use according to the genetics and disease pathophysiology. The issue here has been that kinase inhibitors, for not always rational reasons, have always been perceived to be not safe enough to be used for chronic treatment as it is often the case in non-oncological indications. While the regulatory hurdles to approve kinase inhibitors in indications outside of oncology are much higher there is an intensive search for kinase targets and kinase inhibitors outside the oncological arena. This well documented effort is shown in the table below. For non-oncological indications there is the pipeline of kinase inhibitors that are at various stages of preclinical and clinical development. In particular, the JAKinibs are being pushed for RA and other indications (see also presentation of Ian McInnes).